

Case studies and cost-benefit analysis of HER2 and TPMT in Four EU member states

PART 2 OF AN ESTO STUDY ON PHARMACOGENETICS AND PHARMACOGENOMICS: STATE OF THE ART AND SOCIAL AND ECONOMIC IMPACTS

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1. Introduction

1.1 Objectives and Scope

This report is Part 2 of the ESTO study on “Pharmacogenetics and Pharmacogenomics: state of the art and social and economic impacts”. The objective of this report is to provide insight into the practical aspects of the implementation of pharmacogenetics and pharmacogenomics in Europe, its costs and benefits and its associated socio-economic issues. This has been done through two cases of pharmacogenetics and pharmacogenomics applications-tests already in use: TPMT and HER2. This study focuses on highlighting important commonalities and differences in the way these two tests and their related drugs have been implemented in four European countries (Germany, Ireland, the Netherlands and the UK) and their socio-economic aspects.

The other parts of this study are:

Part 1 of the ESTO study focusing on mapping key actors, trends and outputs of academic and industrial research and development in the field of pharmacogenetics and pharmacogenomics.

Part 3 focusing on the regulatory regimes surrounding the development and clinical application of Pharmacogenetics and Pharmacogenomics of the USA, EU and the four EU member states.

1.2 Pharmacogenetics and Pharmacogenomics

The field of pharmacogenetics has a history dating back to the 1950s. The term pharmacogenetics is generally associated with inheritance, for example Weilshboum R and Wong L (2004) define pharmacogenetics as ‘the study of the role of inheritance in inter-individual variation in drug response’. Pharmacogenomics is a term that emerged in the late 1990s and is often associated with industrial application of genomics in drug discovery (Sneddon 1999). While many have struggled to find agreement on the precise meaning of the terms pharmacogenetics and pharmacogenomics (for example see Sneddon 1999, Lindpaintner 2002, FDA 2002, Hedgecoe 2004), in this report we use the term PGx to refer collectively to the science and technologies associated with dividing patients or populations into groups on the basis of their therapeutic requirements using a genetic test. We therefore include activities related to classical pharmacogenetics as well as studies of gene expression or methods of disease stratification related to predicting drug response. Although more recently PGx has become associated with molecular genetics, we do not limit our definition of a genetic test to methods that rely on direct DNA analysis, but also include phenotypic tests (such as those operating at the protein, metabolite or other biomarker level such as IHC tests and other non-genetics based test methods) where these may be used to reveal an underlying genetic change relevant

during the therapeutic decision making process. We also include both heritable and somatic change as relevant to the field of PGx.

1.3 Qualitative and quantitative aspects of the case studies

In order to gain insight into the practical aspects of implementation PGx in Europe, and associated socio-economic issues two cases that deal with PGx testing that are already in use in clinical practice will be evaluated to reveal possible economic and social issues. These are HER2-testing (efficacy of trastuzumab) and TPMT testing (safety of thiopurine drugs). These two case studies cover two of the main applications of pharmacogenetics, i.e. the improvement of efficacy and the reduction of adverse effects, and could therefore be used to gain insight into the current and past social and economic issues. Four countries have been selected for these case studies: Germany, Ireland, the Netherlands and United Kingdom.

The case studies have a quantitative part dealing with a cost-benefit assessment in the four EU countries for TPMT use in Leukaemia, and Her-2 use in breast cancer. These are presented in Chapter 2.

Chapter 3 presents the four qualitative country case studies for Her2 testing. Chapter 4 presents four qualitative country case studies for TPMT testing. The qualitative part of the case studies has the following structure. First, the introduction of the tests, and related drugs, into the country is presented and a description of the present state of the art concerning the use of the test and drug is given. It describes how HER2 and TPMT-testing came into being, the development and approval process and the role of specific actors such as clinicians, industry and patient organisations.

There are a number of specific social and economic issues related to each of the two tests, such as quality assurance and control, economic aspects (such as impacts of the tests on the drug market), reimbursement situation (who pays for the expensive test and drugs) and social and ethical issues mostly dealing with the patients view and attitudes to wards the tests), informed consent and perception. Chapter 5 draws conclusions from the cost-benefit assessment and both case studies.

The following sections of this introduction chapter provide background information of both cases on basis of a literature study and present the current scientific insights (based on: Ibarreta and Woelderink, 2004).

1.4 Introduction to the case of ‘ Human Epidermal Growth Factor Receptor’ (HER2)

The development of new drugs has traditionally been a process of trial and error. However, advances in genetic research and pharmaceutical sciences have led to the possibility for a better identification of targets for pharmaceuticals in the last decade.

Simultaneously, the possibility had appeared to apply so called ‘monoclonal antibodies’ which are widely used in diagnostics, for specific targeting in the human body. From the first monoclonal antibody from Kohler and Milstein in 1975, it has taken approximately 25 years for their therapeutic applications to become incorporated into clinical practice.

The cloned Human Epidermal-Growth-Factor Receptor 2 (HER2), associated with a form of metastatic breast cancer, appeared as a potential monoclonal-antibody target in 1985. It has many of the properties required for such a target; it is overexpressed on the surface of tumour cells and not on normal cells, it has an extracellular domain that is readily accessible, and expression of the receptor is stable in primary tumour tissues and metastatic deposits. As a result the humanized IgG1 monoclonal antibody ‘trastuzumab’, with high affinity and specificity for HER2 was developed, and clinical trials were started in 1992. In 1998 the drug was approved in the US by the FDA as ‘Herceptin’. This drug was able to get a fast track approval status for two reasons: it demonstrated efficacy in patients previously resistant to more conventional treatments and a diagnostic test was able to identify the patients that were expected to benefit from Herceptin. Herceptin and its diagnostic ‘HercepTest’ were approved in Europe in the year 2000 by the EMEA’s centralized procedure.

The HercepTest is the first example of a pharmacogenomic test that is marketed along with a drug. Some have argued about the genetic nature of this test. The OECD-definition says: “*Genetic testing is testing for variations in germline DNA sequences, or for products/effects arising from changes in heritable sequences, which are predictive of significant health effects.*” The HercepTest detects an overexpression of receptors, caused by the presence of more than 2 HER2-genes. Although the presence of these extra genes has a somatic nature, we are still talking about the measurement of the product from these genes. In this sense, the HercepTest can and will be considered as a pharmacogenomic test.

Herceptin is approved for the treatment of breast cancer-patients. More specifically, the two indications for Herceptin are stated as follows:

- As a monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane, unless patients are unsuitable for these treatments;
- In combination with paclitaxel (chemotherapy) for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.

Herceptin should only be used in patients whose tumours have HER2-overexpression, determined by immunohistochemistry (IHC). The HER2 status can also be determined by Fluorescence In Situ Hybridisation (FISH).

HER2, encoded by the HER2/neu proto-oncogene is one of a family of receptors that have important roles in the control of how cells grow, divide and repair themselves. The HER2 gene directs the production of special proteins, called HER2 receptors. About 20-

30% of all females with breast cancer have an over-expression of HER2-receptors on the surface of the breast-cancer cells. Such tumours are termed 'HER2-positive'.

Patients who are considered HER2-positive have HER2 gene amplification or HER2 protein over-expression. Cancers with too many copies of the HER2 gene or too many HER2 receptors tend to grow fast. This form of metastatic breast cancer is therefore more aggressive than other forms; the women have a higher probability of metastasis or spreading of the cancer; resistance to treatment with conventional chemotherapy; and a significantly shorter life expectancy. As a consequence it is crucial to carefully define the genetic background of the tumour to ensure the appropriateness of the drug.

There are two tests in the FDA label to determine HER2 status and select patients for treatment with Herceptin. The first approved was an immunohistochemistry (IHC) test, the HercepTest, which measures the level of expression of the HER2 protein. The possible outcomes of the test are reported as numbers from 0 to 3+, with 0 representing no overexpression and 3+ representing high overexpression. Only 3+ is defined as HER2 positive. The most recently approved method, FISH, detects the underlying gene alteration in the patient's tumour cells. FISH makes the number of HER2/neu gene copies visible. In healthy cells, there are 2 or more copies of the HER2/neu gene per chromosome. If FISH detects more than 2 copies of the HER2 gene, it means that the cell is abnormal and is HER2-positive. This abnormality is also referred to as HER2 gene amplification. The results of the FISH test can be reported as "positive" or "negative."

Recent comparison of FISH and IHC shows that FISH appears to be superior at providing prognostic information with respect to the detection of higher risk breast cancers (Mass et al, 2001). Unfortunately, it is expensive and requires additional equipment and training to that which is at present routinely found in most laboratories. For this reason, different parties recommend that only IHC result of 2+ (which represents a little over-expression of HER2) should be retested with FISH to prevent false-negative outcomes (Ellis et al, 2004). However, the FISH test is not included in the label in Europe.

The quality of the detection methods must be good to prevent false-negative outcomes and the results should be reproducible. (A false-negative result implies that patients do not receive the treatment while they do are HER2-positive, and a false positive result implies that patients receive the treatment inappropriately). Recent findings suggested that laboratories with more than 100 tests per month were more reliable than smaller laboratories (Paik et al). Another study stated this number as 250 tests per year for assurance of expertise (Ellis et al, 2004). For these reasons, not only the predictive value of detection methods as well as the performance of laboratories must be assured. It can also be argued that labs which do more tests are more likely to be part of a QA scheme, which implies that they have standard operating procedures for the test, which make them better performers.

Herceptin has proven to be effective in clinical trials. After one year of therapy, significantly more of the patients given Herceptin plus chemotherapy survived (79% of patients) versus those given chemotherapy alone (68% of patients). In a second trial for

Herceptin as a monotherapy, a reduction in tumour size was seen in 14% of patients treated with Herceptin alone. When a physician does decide to screen a patient some of the tumour tissue is taken and sent to a laboratory for the test. When the tumour appears to be HER2-positive, a combination therapy of Herceptin and chemotherapy has proven to be the most effective in terms of survival- and response-rates. Patients who receive Herceptin as a monotherapy are less likely to experience the side effects typical of other types of treatments, such as hair loss, but are exposed to possible cardiotoxicity-events.

A study from Osoba *et. al*, (2002) to the quality of life in patients treated with chemotherapy or with Herceptin plus chemotherapy points out that there is a significant increase in the quality of life by adding Herceptin to the chemotherapy. Therapy is likely associated with the decreases in tumor. Taken together with the significant improvements in disease response rates, survival and median duration of response this provides additional support for the benefit of trastuzumab combined with chemotherapy (as compared with chemotherapy alone), for the treatment of HER-2 positive breast cancer.

1.5 Introduction to the case of ‘Thiopurine methyltransferase’ (TPMT)

Gertrude Elion and George Hitchings, who have collaborated since 1945, demonstrated differences in nucleic acid metabolism between normal human cells, cancer cells, protozoa, bacteria and virus. On the basis of such differences a series of drugs were developed that block nucleic acid synthesis in cancer cells without damaging the normal human cells. During 1950-51's they developed the chemotherapeutic drugs thioguanine and 6-mercaptopurine for the treatment of leukaemia. After this they tried to improve the therapeutic properties of 6-mercaptopurine by using sulphur-substituted compounds. The result was azathioprine (1957) which replaced mercaptopurine as an inhibitor of the immune response. For a long time azathioprine was the only drug available to prevent rejection of transplanted organs. It is still used for that purpose but also for the treatment of autoimmune diseases.

In 1953 the ‘wonder drug’ 6-mercaptopurine (6MP) was marketed in the US, and later in Europe, under the brand name ‘Purinethol’. The expectations of this drug were high in the medical world, and a lot of children were cured from their leukaemia. About 20 years ago, however, researchers discovered that the drug could be extremely toxic for 0,3% of the patients. The same goes for azathioprine, marketed in Europe and the US in 1968 as ‘Imuran’, where toxicity and fatal sepsis were reported in transplant-patients. In the 1990's a DNA test to predict toxicity, became available in the USA. It is argued that the narrow therapeutic index (small changes in the dosage level may cause toxic results) of these so-called thiopurine drugs, together with their highly variable pharmacokinetics, makes them an ideal class of drug for dosage individualization.

Therapeutic indications of Thiopurine drug

Thiopurine agents are used in the treatment of neoplastic disease, autoimmune disease, anti-cancer and organ transplants. More specified the indications are stated as follows in table 1.

Table 1 Indications of thiopurine drugs

Purinethol (6-Mercaptopurine)	Lanvis (6-thioguanine)	Imuran (azathioprine)
Acute Lymphatic Leukemia	Acute Lymphatic Leukemia	Renal Homotransplantation
Acute Myelogenous Leukemia	Acute Myelogenous Leukemia	Rheumatoid Arthritis
	Chronical myelogenous leukemia	(Azathioprine is a 'pro-drug' that is converted into 6-mercaptopurine when it comes into the body)

Thiopurine Methyltransferase is a cytoplasmic enzyme expressed by the TPMT gene. On this gene, at least three mutations are discovered and a further polymorphism was recently identified within the promoter region. A polymorphism of the gene is (partly) responsible for large inter-individual differences observed in TPMT activity. In pharmacological terms, TPMT is responsible for the metabolism of the thiopurine drugs mentioned above, by means of the catalysis of the s-methylation of these drugs. Since 1989 several studies have confirmed that patients with inherited very low levels of TPMT are at increased risk of thiopurine-induced toxicity. Following this, evidence was also obtained that patients with a very high TPMT activity might display decreased therapeutic efficacy when treated with standard doses of thiopurine drugs.

Detection of TPMT polymorphisms

Because overdosing of thiopurine drugs could have serious implications, like hematological toxicity or fatal sepsis, it is important to know a patient's TPMT level before starting with the therapy.

Table 2 TPMT activity and recommended doses

Genotype	TPMT activity	Population (%)	Thiopurine drug-use
Homozygous H/H	High	89	Standard or higher dose
Heterozygous L/H	Intermediate	11	Reduced dose by 15-50%
Homozygous L/L	Deficient	0,3	No treatment or dose reduced by 90%

Note for Table 2: This population study involved Caucasian patients. If the same study had been conducted in East Asia, this trimodal distribution would not be shown.

For all of the drugs mentioned in Table 2, TPMT activity can be measured in the blood of the patients through several methods. Each of these methods have advantages and disadvantages which are discussed elsewhere in this report (see TPMT case studies in Chapter 4).

The phenotypic assay is carried out using red blood cells as the source of the enzyme, TPMT, and usually uses 6-thioguanine as substrate for the test. The blood is combined with the 6-thioguanine and the quantity of reaction product, 6-methylthioguanine, is then measured by HPLC, by radiochemical assay or by some other chemical method. The amount of reaction product will indicate the level of TPMT.

A red cell count or total cell count is used as a general test to determine the patients response to drug therapy, and is recommended in some literature from the drug manufacturers as a test system to monitor adverse effects. However, it has no relevance to measurement of TPMT.

It is also possible to detect mutations on the TPMT gene with PCR, which is however not used routinely.

Several trials, conducted since 1989, demonstrated a significant correlation between phenotype and adverse events. In genotyping studies however, the vast majority of adverse effects were not caused by TPMT-deficiencies. An overview of six correlation studies is given by van Aken et al. (2003) Although a pharmacogenetic test could prevent people from adverse events, it will not eliminate the need for careful clinical monitoring of side-effects.

Clinical use

In Europe, TPMT testing is used in clinical practice, and CE-marked tests are available. Although a red blood cell count is recommended in the label (of the drug), the performance of a TPMT test is not mentioned. The detection of the TPMT activity occurs by means of home-brew tests as well.

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2. Cost-effectiveness of pharmacogenomics in clinical practice

2.1 Introduction

Although an increasing number of applications of pharmacogenomics are described in the literature, the economic implications of pharmacogenomics have been little explored so far. This may be partly due to the fact that pharmacogenomics is a young field, but clarifying the economic implications of pharmacogenomic treatment strategies may facilitate their implementation, which stresses the necessity of economic evaluations of pharmacogenomic treatment strategies. Other topics, such as ethical and legal aspects, have to be studied as well, before a well-considered decision about implementation can be made.

Analysing the cost-effectiveness of a pharmacogenomic strategy involves the comparison of the cost and effects of the pharmacogenomic strategy compared to current medical practice. Factors that play an important role in this comparison are the genotype of interest, the genomic test, the disease state and the treatment. In general a pharmacogenomic strategy is likely to be cost-effective when (i) the polymorphism under consideration is prevalent in the population and has a high degree of penetrance; (ii) the available genetic test is highly sensitive and specific; (iii) the disease state involves outcomes with significant morbidity or mortality if left untreated; and (iv) the treatment involves significant outcomes and/or costs that can be impacted by genotype-individualised therapy (Flowers & Veenstra, 2004).

Pharmacogenomic strategies for improved clinical treatment regimes can be divided into two main categories: 1) Pharmacogenomic strategies for increasing treatment efficacy and 2) Pharmacogenomic strategies for decreasing toxicity. In this study an example of a cost-effectiveness analysis for both categories will be given. The two examples of pharmacogenetic testing in clinical practice that will be analysed are HER2-testing (efficacy of trastuzumab) in women with metastatic breast cancer and TPMT-testing (safety of thiopurine drugs) in children with acute lymphoblastic leukaemia (ALL).

2.2 Review of cost-effectiveness analysis in pharmacogenomics

Cost-effectiveness analysis is a widely used tool to assess the value of healthcare interventions. Several articles exist that introduce this kind of analysis to the field of pharmacogenomics (Veenstra & Higashi 2000; Phillips et al. 2003; Flowers & Veenstra 2004). However, they are only rarely used in pharmacogenomics. Phillips & Van Bebber (2004) performed systematic review of cost-effectiveness analyses of pharmacogenomic interventions and identified only 11 studies that met their inclusion criteria up to and including July 2004. This means that both the costs and effects of a program were compared with at least one alternative, this comparison was presented as a ratio, and sufficient details were provided for a minimal analysis as described by Gold et al. (1996). In the mean time another cost-effectiveness analysis was published by Winter et al. (2004).

The most commonly examined disease was deep vein thrombosis (n=4) followed by cancer (n=3) and viral infections (n=3). The most frequently examined mutation factor was factor V Leiden (n=5).

The majority of the studies reported a favourable cost-effectiveness ratio for the pharmacogenomic-based strategy (n=7), while two studies reported that the pharmacogenomic intervention was not cost-effective and two were equivocal. Characteristics of the studies are presented in table 3.

Phillip & Bebbler concluded that there have been few evaluations of the economic costs and benefits of pharmacogenomic interventions and they have covered a limited number of conditions.

Table 3 Characteristics of cost-effectiveness analyses of pharmacogenomic interventions

<i>Article</i>	<i>Mutation name</i>	<i>Drug name</i>	<i>Primary outcome measure</i>	<i>Primary cost-effectiveness result</i>
Auerbach et al. (2004)	Factor V Leiden plus other	Warfarin	Cost/QALY gained	Favorable
Creinin et al. (1999)	Factor V Leiden	Oral contraceptive pill	Other	Not favourable
Eckman et al. (2002)	Factor V Leiden	Warfarin	Cost/QALY gained	Equivocal
Elkin et al. (2004)	HER2/neu	Trastuzumab	Cost/QALY gained	Equivocal
Marchetti et al. (2000)	Factor V Leiden	Warfarin	Cost/QALY gained	Favorable
Marchetti et al. (2001)	Factor V Leiden plus other	Warfarin	Cost/QALY gained	Favorable
Marra et al. (2002)	Thiopurine methyltransferase	Azothiopurine	Other	Favorable
Oh et al. (2003)	Thiopurine methyltransferase	Azothiopurine	Other	Favorable
Weinstein et al. (2001)	HIV variants	Highly active antiretroviral treatment	Cost/QALY gained	Favorable
Winter et al. (2004)	Thiopurine methyltransferase	Azothiopurine	Other	Favorable
Wong et al. (1998)	Hepatitis C virus genotypes	IFN- α -2b	Cost/QALY gained	Not favourable
Younossi et al (1999)	Hepatitis C virus genotypes	IFN- α -2b plus ribavirin	Cost/QALY gained	Favorable

2.3 Methods

For both topics of this study, HER2-testing and TPMT-testing, models are developed for the comparison of the costs and effects of the pharmacogenomic treatment strategy with the current medical practice, and the model parameters were identified. The model parameters concern economic, genetic and clinical data.

Subsequently information on model parameters was collected from literature and expert opinions in the different participating countries (Germany, United Kingdom, Ireland and the Netherlands).

The analyses are performed from the societal perspective, the preferred perspective for economic evaluations. This means that all costs and effects are included regardless of who incurs the costs and who obtains the effects (Gold et al. 1996).

Costs are in 2004 euros. When costs were from other years, the effect of price inflation was removed by using the harmonised annual average price indices of the different countries to inflate the data to the year 2004. If cost information was based on published results and no price level was mentioned in an article, the year before publication of the article was used, assuming performing the analysis, writing the article and publication of the article will take one year. Also when costs were in currencies other than Euros, costs were converted into Euros.

Sensitivity analyses are performed in which the values of the model parameters are varied. In this way the degree of influence each parameter had on the cost-effectiveness is studied, and crucial parameters determining the cost-effectiveness of pharmacogenomics are identified.

Both univariate and multivariate sensitivity analyses are performed. In univariate sensitivity analyses, one model parameter at a time is varied. Univariate sensitivity analysis is useful to give insight in the way a model parameter influence the cost-effectiveness. However, looking at one source of uncertainty at a time provides an incomplete estimate of how uncertain the estimated overall cost-effectiveness ratio actually is, as the cost-effectiveness ratio depends on multiple parameters and the interaction of these parameters may imply that the total effect may be something quite different from the simple sum of individual contributions. Therefore, we also performed multivariate sensitivity analyses in which all model parameters are varied together. One approach to perform a multivariate sensitivity analysis is a probabilistic analysis. For both models a probabilistic analysis was performed. Therefore, 100,000 random draws from the probability distributions defined for the model parameters are taken for each model parameter, and the resulting cost-effectiveness ratio for these parameter values is calculated using Crystal Ball, Version 4.0 (Microsoft Corporation). In this way an estimate of the cost-effectiveness ratio's distribution is obtained. Furthermore, information is derived about the influence of the uncertainty around the individual parameters on the uncertainty in the cost-effectiveness ratio.

2.4 TPMT

6-Mercaptopurine (6-MP) is administered to children with acute lymphoblastic leukaemia (ALL). However, some of the patients experience adverse reactions, including myelosuppression. There is a recognized association between myelosuppression and diminished activity of thiopurine methyltransferase (TPMT).

Patients who have one mutant allele for the TPMT enzyme which is associated with reduced activity and patients that are homozygous for these mutations and have very low activity, entail a high risk of myelosuppression. However, TPMT activity is not the sole mechanism.

TPMT activity can be assessed indirectly by measuring red blood cell enzyme activity or predicted by genotype analysis. In this analysis we will focus on the PCR test, although this test is not used routinely in each country.

Current practice is to monitor the blood count regularly and to reduce or to stop administering 6-MP to children with severe adverse reactions. However, this is not infallible as adverse reactions can develop suddenly and can result in death. Screening for TPMT will detect children that are at high risk for adverse reactions and may prevent severe adverse reactions.

We studied the cost-effectiveness of screening for TPMT prior to initiation of 6-MP treatment for children with ALL.

Material

Model parameters were identified and searched for in the literature and enquired by experts in each country. In general, not much information on the parameters for the TPMT model was specifically available for children with ALL. Therefore, estimates from pharmacoeconomic studies on other thiopurine drugs are frequently used (Marra et al. 2002; Oh et al. 2004; Winter et al. 2004).

TPMT activity in general population

The distribution of TPMT activity in the population differs with respect to ethnicity. For this study we used the distribution as found in Caucasians. The majority of the individuals (88.7%) have high TPMT activity, corresponding to the homozygous wild-type genotype. Approximately 10% of the population are heterozygotes at the TPMT gene locus and have intermediate TPMT activity. Homozygotes with two TPMT mutant alleles have deficient TPMT activity and account for 0.3% of the population (el-Azhary, 2003).

Adverse events

Myelosuppression was reported to occur in 1-11% of the patients by one of the experts. Sanderson et al. (2004) reported a frequency of 1.4-5%. Winter et al. (2004) assumed the frequency of leucopenia in adults with inflammatory bowel disease treated with thiopurine drugs to be 3.2%, based on the results of seven studies. For patients with rheumatological conditions treated with azathioprine, Marra et al. (2002) assumed the probability of haematological cytopenia to be 0.09.

Other adverse events include allergic reactions (2.3%), nausea, vomiting, lack of appetite, diarrhoea (1.4-5%), pancreatitis (1.4-5%), and infections (7%). These adverse events

were not included in the costs analysis, as their costs are assumed to be minor by comparison.

However, prospective evaluation of TPMT activity will not eliminate all cases of myelosuppression. Marra et al. (2002) assumed 50% of the cases of haematological toxicity could be eliminated by screening for TPMT and dosage reduction. Sanderson et al. (2004) report a percentage of 29% of the adverse reactions to be the result of overdosing 6-MP, based on the study of Colombel et al. 2000). Based on the studies that Winter et al. (2004) cite (Colombel et al. 2000, Ansari et al 2002, Schwab et al 2002), they assume an association of leucopenia with TPMT deficiency of 32%.

Myelosuppression may lead to death. Winter et al. (2004) assumed that in case of TPMT screening of 1,000 patients 1 death may be avoided. This indicates that when we perform our analysis for children that are on average 8 years old, and assume that the life expectancy is 75 years, screening of 1,000 patients will result in 67 life years gained, or with a discount percentage of 3%, 29.6 life years gained.

PCR test

Oh et al. (2004) assumed the sensitivity and specificity of PCR genotyping to be 96.3% and 100%, respectively. Marra et al. (2002) used slightly different estimates for the sensitivity and specificity of the PCR test of 95.2% and 100%, respectively.

Costs

Large differences were found in the costs of the PCR test, consisting of the material and personnel cost of performing the PCR test, reported by the different countries. The United Kingdom reported an amount of GBP 20-30 (EUR 29-44). In Germany a range from EUR 32-300 was reported. For the Netherlands the cost of PCR testing are assumed to be EUR 175, this amount is based on tariffs (NHTA, 2004). In Ireland the estimated cost per test is EUR 250. If the PCR test was in routine clinical use, this would significantly reduce.

In other cost-effectiveness analyses amounts of CAD 100 (EUR 72 price level 2004, Marra et al. 2002) and GBP 30 (EUR 44 price level 2004, Winter et al. 2004) were reported.

The costs of adverse events were based on hospital days and outpatient visits, as other costs are minor by comparison. A dutch expert estimated that 10% of the patients with serious adverse events need inpatient treatment of at least 7 days. This amounts to EUR 2549, price level 2004 (Oostenbrink et al. 2004). The other 90% of the patients are managed as an out-patient. As they already have frequent outpatient visits, this will not result in additional costs. The average cost per patient for the Dutch situation can be estimated at EUR 255.

Winter et al. assumed that two-thirds of patients suffering significant leucopenia could be managed as an out-patient, requiring two additional visits at GBP 115 (EUR 335, price level 2004). The remaining part of the patient would require hospital admission because of infective complications. Assuming them to stay for 10 days in a haematology ward at GBP 402/day, results in a total amount of GBP 4020 (EUR 5863, price level 2004) for

these patients. The average cost per patient can be calculated to be EUR 1551 (price level 2004).

Tavadia et al. (1999) reported costs of adverse events of CAD 7757.69 (EUR 5578, price level 2004) per case.

Marra et al. (2002) assumed that 50% of the patients with adverse events would need to be hospitalized, for an average duration of 10 days amounting to CAD 2679 (EUR 1925, price level 2004). For the 50% of the patients able to be managed as outpatients the costs were assumed to be CAD 790 (EUR 568, price level 2004). The average cost per patient amount to EUR 1247.

Base case analysis

In table 4 the values of the model parameters used in the base case model are presented. The values are based on the values for the parameters found in literature and reported by experts as described above. The base case values are in between the range described for a model parameter.

Table 4 Base case value parameters TPMT model

<i>Model parameter</i>	<i>Base case value</i>
Homozygous wild-type	88.7%
Heteroygous	10.0%
Homozygous mutant	0.3%
Probability of myelosuppression	0.03
Adverse events associated with TPMT	32%
Mortality prevented per person screened for TPMT	0.001
Sensitivity PCR test	95.2%
Specificity PCR test	100%
Costs PCR test (EUR price level 2004)	150
Costs of myelosuppression (EUR price level 2004)	1000

Sensitivity analysis

In the sensitivity analysis the values of the model parameters are varied, in order to determine the degree of influence each parameter has on the cost-effectiveness. The lower and upper values are based on the values for the parameters found in literature and reported by experts as described above. The lower and upper values represent the lower respectively upper bound of the range described for a model parameter (see Table 5).

Table 5 Lower and upper values parameters TPMT model

Model parameter	Sensitivity analysis	
	Lower	Upper
Probability of myelosuppression	0.01	0.1
Adverse events associated with TPMT	20%	50%
Mortality prevented per person screened for TPMT	0.0001	0.003
Sensitivity PCR test	76.2%*	99.9%*
Costs PCR test (EUR price level 2004)	30	300
Costs of myelosuppression (EUR price level 2004)	250	1500

* Marra et al. 2002

Results

Base case analysis

We performed the cost-effectiveness analysis for a hypothetical cohort of 100,000 children with ALL. Of these 100,000 children, 3000 will experience myelosuppression, of which 960 cases are related to TPMT deficiency. Assuming a sensitivity of the PCR test of 95.2% indicates that 914 of these adverse events may be prevented by screening for TPMT prior to initiation of 6-MP treatment.

The savings due to the prevention of adverse events amount to EUR 931,920, while the cost of PCR tests for 100,000 children with ALL are EUR 15,000,000, indicating the cost of TPMT screening to be EUR 141 per child with ALL.

If we were to avoid one death per 1,000 children screened, we save 6700 life-years by screening 100,000 children, costing EUR 2,102 per life-year saved. When discounted at 3%, the cost per life-year saved rises to EUR 4,760 per life-year saved.

Sensitivity analysis

In a univariate sensitivity analysis we varied one variable at a time (see Table 6). Using the lower values for the probability of myelosuppression, adverse events associated with TPMT, mortality prevented per person screened for TPMT, sensitivity of the PCR test and the costs of myelosuppression leads to a less favourable cost-effectiveness ratio. Although the changes in cost-effectiveness ratio for most of the parameters were small, the costs per life year gained increased considerably if the lower value is used for the mortality prevented per person screened for TPMT. In contrast with the other parameters, lowering the costs of the PCR test leads to a more favourable cost-effectiveness ratio. Also for the costs of the PCR test the change in cost-effectiveness was considerably. Using the upper values of the parameters had the opposite effect.

Table 6 Univariate sensitivity analysis: cost-effectiveness ratio, expressed as costs per life-year gained, for lower and upper values of model parameters, with 3% discounting

<i>Model parameter</i>	<i>Lower value</i>	<i>Upper value</i>
Probability of myelosuppression	4,965	4,039
Adverse events associated with TPMT	4,875	4,615
Mortality prevented per person screened for TPMT	47,596	4,744
Sensitivity PCR test	4,821	1,587
Costs PCR test	705	9,829
Costs of myelosuppression	4,991	4,605
Baseline	4,760	

In a multivariate sensitivity analyses we varied all model parameters included in the sensitivity analysis (see Table 3) together. Under the assumption that all of the model parameters mentioned in Table 3 are independent from each other, we can construct a set of extreme parameter values that yield the highest and the lowest cost-effectiveness ratios. To construct the highest cost-effectiveness ratio, we took the lower values for the probability of myelosuppression, the percentage adverse events associated with TPMT, the mortality prevented by TPMT screening and the costs of myelosuppression. For the costs of the PCR test, we used the upper value. This resulted in a cost-effectiveness ratio of €44,719 per life-year saved (€101, 240, 3% discounting). On the opposite, taking the upper values for the probability of myelosuppression, the percentage adverse events associated with TPMT, the mortality prevented by TPMT screening and the costs of myelosuppression and the lower value for the costs of the PCR test resulted in both financial savings and a gain in life-years.

Subsequently, we performed a probabilistic analysis in which we assumed a uniform distribution for the parameters between the lower and upper value presented in Table 4. In this way we estimated that only with a probability of 1.2% savings will be obtained. Also we obtained information about the parameters that had the most important influence on the cost-effectiveness ratio. The most important parameters are the costs of the PCR test and the mortality prevented by TPMT screening. The uncertainty around these estimates cause each 49% of the uncertainty in the costs per life year gained (irrespective of discount percentage).

The other uncertainty around the costs per life year gained is caused by the percentage adverse events prevented by screening and the costs of adverse events (both explain a percentage of 1% of the uncertainty around the costs per life year gained).

2.5 HER2

Trastuzumab has been shown to benefit metastatic breast cancer patients whose tumors exhibit HER2 protein overexpression or gene amplification (Slamon, 2001). Tests currently used to determine HER2 status and select patients for treatment with Herceptin, are an immunohistochemistry test (IHC) and a fluorescence in situ hybridisation (FISH) test. The IHC test measures the amount of the HER2 protein present. The possible outcomes of the test are reported as number from 0 to 3+, with 0 representing no overexpression and 3+ representing high overexpression. The FISH test detects the underlying gene alteration in the patient's tumor cells. The results of the FISH test can be reported as 'positive' or 'negative'.

The FISH test appears to be the most reliable method of assessment. However, it is far more expensive than the IHC test. A number of combinations of the IHC test and FISH test can be studied in order to identify the most cost-effective test-treatment strategy. In this study the following strategies will be studied in comparison with chemotherapy alone for all women with metastatic breast cancer, see Table 7.

Table 7 *Test-treatment strategies for women with metastasized breast cancer*

Strategy	Initial test	Confirmatory test	Treatment
1	IHC	None	Chemotherapy + trastuzumab if IHC 3+ Chemotherapy otherwise
2	IHC	None	Chemotherapy + trastuzumab if IHC 2+ Chemotherapy otherwise
3	IHC	FISH if IHC 2+ or IHC 3+	Chemotherapy + trastuzumab if FISH+ Chemotherapy otherwise
4	IHC	FISH if IHC 2+	Chemotherapy + trastuzumab if FISH+ Chemotherapy + trastuzumab if IHC 3+ Chemotherapy otherwise
5	FISH	None	Chemotherapy + trastuzumab if FISH+ Chemotherapy otherwise
6	none	None	Chemotherapy + trastuzumab for all

Chemotherapy can consist of treatment with paclitaxel or with anthracycline/cyclophosphamide. We assume that all patients receive paclitaxel, given that anthracycline-based therapy is associated with a much greater risk of cardiac toxicity among patients receiving trastuzumab.

Material

Model parameters were identified and searched for in the literature and enquired by experts in each country.

Percentage of women with HER2 overexpression

About 20-30% of all females with breast cancer have an overexpression of HER2-receptors on the surface of the breast cancer cells (Slamon, 1987; Slamon, 1989).

Prognosis of metastatic breast cancer

In the model four groups of women with metastatic breast cancer can be distinguished: HER2 positive women receiving chemotherapy, HER2 positive women receiving chemotherapy and trastuzumab, HER2 negative women receiving chemotherapy and HER2 negative women receiving chemotherapy and trastuzumab. The median survival of women with metastatic breast cancer who are HER2 negative and receive chemotherapy (paclitaxel) was found to be 27.5 months (95% CI = 17.1 to 35.2 months) by Konecny et al (2004). In a trastuzumab randomized trial nearly equivalent response rates were found among patients with a negative FISH result (Mass et al. 2000; Mass et al. 2001). Therefore, we assumed that trastuzumab provided no additional benefit in HER2 negative women (Elkin et al. 2004).

Slamon et al (2001) estimated the median overall survival in women with HER2 positive tumors treated with chemotherapy to be 18.4 months. This estimate is in the 95% CI for the survival found by Konecny et al. 2004 (15.3 to 27.3 months). The addition of trastuzumab to treatment was associated with a longer overall survival (median 22.1 months, Slamon et al. 2001).

Quality of life

Osoba et al (2002) studied the effects on quality of life of combined trastuzumab and chemotherapy in women with metastatic breast cancer. They found no significant improvement in quality of life for patients on chemotherapy plus trastuzumab compared to those on chemotherapy alone.

Earle et al. (2000) performed a systematic review of cost-utility assessments in oncology. In this study the utility value for metastatic breast cancer in different age groups, was reported between 0.16 and 0.85.

Tests

Elkin et al. (2004) identified 10 studies that compared the IHC test (HercepTest, DAKO), with FISH, used in accordance with the test manufacturers' instructions, on a series of unselected cases, and reported results in adequate detail. On the basis of these studies, they calculated the average test characteristics, with each study's estimate weighted by the respective sample size of FISH-positive and FISH-negative cases. They assumed that the FISH test was a gold standard for HER2 status. The results are presented in table 8.

Table 8 HercepTest (IHC) characteristics compared with FISH [95% confidence interval(CI)]

	<i>IHC 0,1+</i>	<i>IHC 2+</i>	<i>IHC 3+</i>
FISH+	0.079 [0.025, 0.134]	0.250 [0.168, 0.332]	0.671 [0.547, 0.795]
FISH -	0.843 [0.779, 0.908]	0.140 [0.081, 0.200]	0.017 [0.004, 0.029]

Costs

The reported costs of the IHC test (including material and personnel costs) vary significantly, from GBP 70 (EUR 103, United Kingdom) to EUR 190 (Ireland). The costs reported by Germany EUR 127 (public institutions) and EUR 167 (private institutions) are in between. For the Netherlands only the material costs are reported (EUR 30). In the literature lower costs are reported of USD 85 (EUR 68 price level 2004, Elkin et al. 2004) and DEM 188 (EUR 102 price level 2004, Hehl 2001).

The same differences are seen in the costs of the FISH test reported. The reported costs of the FISH test (including material and personnel costs) vary between GBP 150 (EUR 220, United Kingdom) to EUR 495 in The Netherlands. The reported costs from Ireland (EUR 250) and Germany (EUR 257, public institutions and EUR 398, private institutions) are within this interval. In the literature the costs of the FISH test amount to USD 382 (EUR 292 price level 2004, Elkin et al. 2004) and DEM 150 (EUR 82 price level 2004, Hehl 2001).

The additional costs of treating women with metastasized breast cancer with chemotherapy and trastuzumab instead of chemotherapy alone, consist of direct medical costs (cost of treatment with trastuzumab) and non medical costs (as for example patient time costs, travelling costs, cost of sick leave). It appeared to be beyond the scope of this study to estimate the additional non medical costs which is a prerequisite for performing an economic analysis from the societal perspective. Therefore, we restricted the additional cost of treating women with chemotherapy and trastuzumab instead of chemotherapy alone to the direct medical costs.

For the Dutch situation the additional costs are reported to consist of an average number of six cures with three weekly treatments with trastuzumab. The costs of one treatment with trastuzumab amount to EUR 656 (assuming a mean weight of 75 kg, Health Care Insurance Board, 2005). Furthermore, patients get dexamethason against side-effects of trastuzumab. The costs of dexamethason are EUR 22 per treatment (8 ml). Every first week of a cure consist of treatment with chemotherapy and trastuzumab, the second and third week of a cure consist of administering trastuzumab only. This means that an additional number of 12 outpatient visits are needed for treatment with chemotherapy and trastuzumab compared to chemotherapy alone. The costs of an outpatient visit amount to EUR 72 (Oostenbrink et al. 2004). The resulting total additional medical costs are EUR 13,068.

In the United Kingdom, after loading 8-20 cycles of trastuzumab are administered to a patient. The costs of trastuzumab are GBP 400 (EUR 589, expert opinion) per treatment. Assuming an average of 15 treatments, the costs of trastuzumab amount to GBP 6,000 (EUR 8,842). This corresponds to the amounts of GBP 5,296 (price level 2000) and GBP 4,235 (price level 2003) reported by respectively Lewis et al. (2001) and the Department of Public Health (2004). Furthermore, an echocardiogram is made every 12 weeks. For an average of four echocardiograms at GBP 89 (Department of Health, 2004; EUR 133 price

level 2004) per echocardiogram, this amounts to EUR 531. The additional medical costs in the United Kingdom result in a total of EUR 6,531.

Base case analysis

In table 9 the values of the model parameters used in the base case model are presented. The values are based on the values for the parameters found in literature and reported by experts as described above. The base case values are in between the range described for a model parameter.

Table 9 Base case model parameters

<i>Model parameter</i>	<i>Base case value</i>
% women with HER 2 overexpression	25%
Median survival women with metastatic breast cancer, HER 2 negative, treated with chemotherapy (months)	27.5
Median survival women with metastatic breast cancer, HER 2 negative, treated with chemotherapy and trastuzumab (months)	27.5
Median survival women with metastatic breast cancer, HER 2 positive, treated with chemotherapy (months)	18.4
Median survival women with metastatic breast cancer, HER 2 positive, treated with chemotherapy and trastuzumab (months)	22.1
Quality of life of women with metastatic breast cancer treated with chemotherapy	0.5
Quality of life of women with metastatic breast cancer treated with chemotherapy and trastuzumab	0.5
Probability IHC 2+ in FISH + women	0.250
Probability IHC 2+ in FISH – women	0.140
Probability IHC 3+ in FISH + women	0.671
Probability IHC 3+ in FISH – women	0.017
Costs IHC test (EUR price level 2004)	130
Costs FISH test (EUR price level 2004)	250
Additional medical costs treatment chemotherapy and trastuzumab compared to chemotherapy alone (EUR price level 2004)	13,000

Sensitivity analysis

In the sensitivity analysis the values of the model parameters are varied, in order to determine the degree of influence each parameter has on the cost-effectiveness. The lower and upper values are based on the values for the parameters found in literature and reported by experts as described above. The lower and upper values represent the lower respectively upper bound of the range described for a model parameter (see Table 10).

Table 10 Lower and upper values parameters TPMT model

Model parameter	Sensitivity analysis	
% women with HER 2 overexpression	20%	30%
Median survival women with metastatic breast cancer, HER 2 negative, treated with chemotherapy (months)	17.1	35.2
Median survival women with metastatic breast cancer, HER 2 negative, treated with chemotherapy and trastuzumab (months)	17.1	35.2
Median survival women with metastatic breast cancer, HER 2 positive, treated with chemotherapy (months)	15.3	27.3
Median survival women with metastatic breast cancer, HER 2 positive, treated with chemotherapy and trastuzumab (months)	16	28
Quality of life of women with metastatic breast cancer treated with chemotherapy	0.2	0.8
Quality of life of women with metastatic breast cancer treated with chemotherapy and trastuzumab	0.2	0.8
Probability IHC 2+ in FISH + women	0.168	0.332
Probability IHC 2+ in FISH – women	0.081	0.200
Probability IHC 3+ in FISH + women	0.547	0.795
Probability IHC 3+ in FISH – women	0.004	0.029
Costs IHC test (EUR price level 2004)	70	190
Costs FISH test (EUR price level 2004)	100	500
Additional medical costs treatment chemotherapy and trastuzumab compared to chemotherapy alone (EUR price level 2004)	6.500	26.000

Results

Base case analysis

We performed the cost-effectiveness analysis for a hypothetical cohort of 100,000 women with metastasized breast cancer for the strategies mentioned in table 7. The results are presented in table 11.

Also the costs and effects of the different treatment strategies are compared to the costs and effects of the baseline strategy (all women receive chemotherapy) in Figure 1. From figure 1 it can be concluded that only strategy 3 (use FISH as confirmation of all positive IHC results) and strategy 5 (use FISH alone) are efficient strategies. These are strategies for which no alternative policy exists that result in more life-years gained for lower costs.

The incremental cost-effectiveness of strategy 3 compared to the baseline strategy amount to EUR 90,500 per QALY gained. Strategy 5 will result in a gain of 609 QALYs per 100,000 women with metastasized breast cancer compared to strategy 3, however at additional costs of EUR 29 million. This results in incremental cost-effectiveness ratio of EUR 95,200 per QALY gained for strategy 5 compared to strategy 3.

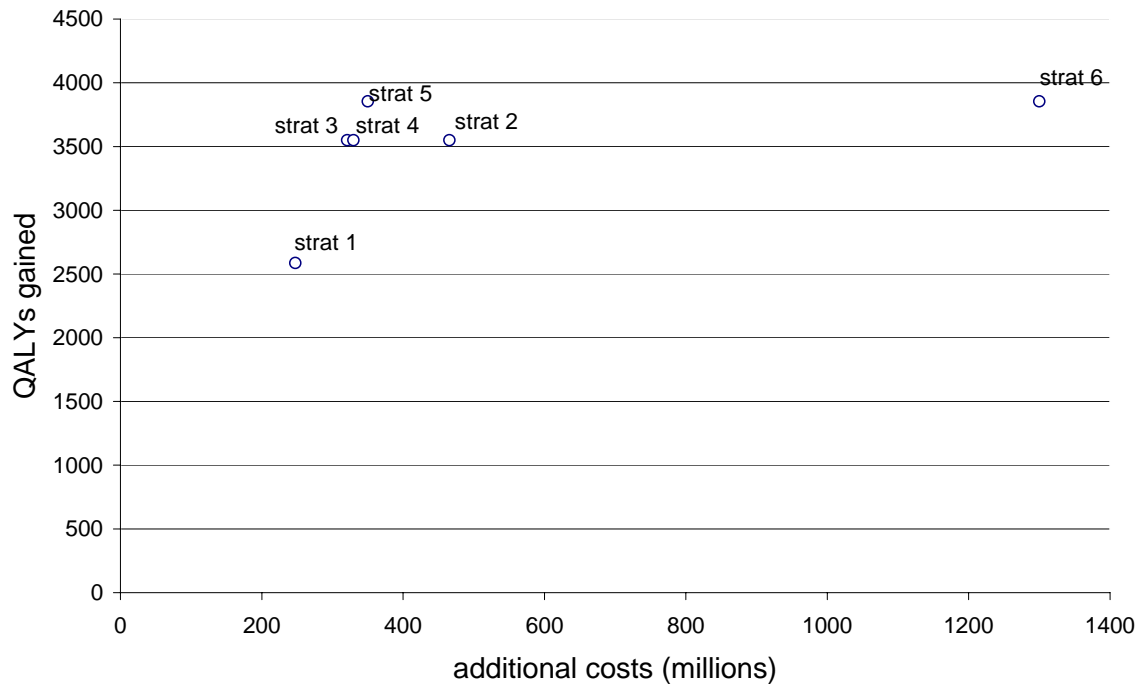
Table 11 Costs (Euros) and effects of the different treatment strategies (see Table 5) for a cohort of 100,000 women with metastasized breast cancer (no discounting, price level 2004)

	<i>Baseline*</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>
Costs initial testing (millions)	0	13	13	13	13	25	0
Costs confirmatory testing (millions)	0	0	0	9	17	0	0
Additional costs treatment** (millions)	0	235	452	299	299	325	1300
Total additional costs (millions)**	0	248	465	321	330	350	1300
Life years	210,208	215,381	217,308	217,308	217,308	217,917	217,917
QALYs	105,104	107,690	108,654	108,654	108,654	108,958	108,958
Cost per life year gained**		47,900	65,600	45,200	46,400	45,400	168,700
Cost per QALY gained**		95,800	131,100	90,400	92,800	90,800	337,300

* All women with metastasized breast cancer receive chemotherapy

** Compared to the baseline strategy

Figure 1 Costs and effects of different treatment strategies (see Table 5) for a cohort of 100,000 women with metastasized breast cancer compared to a strategy in which all women receive chemotherapy



Sensitivity analysis

In a univariate sensitivity analysis we varied one variable at a time. Using the lower values for the percentage of women with HER2 overexpression, the probability of IHC 2+ test results in FISH+ women and the probability of IHC 3+ in FISH+ women result in a less favourable cost-effectiveness ratio. For the probability of IHC 2+ test results in FISH – women, the probability of IHC 3+ test results in FISH – women, the costs of the IHC test, the costs of the FISH test and the additional medical costs of treatment with trastuzumab, lower values leads to a more favourable cost-effectiveness ratio. Varying the median survival leads to differences in the expected cost-effectiveness ratio, if the difference in median survival between women treated with and without trastuzumab changes. If the difference in median survival between women treated with and without trastuzumab becomes smaller, the cost-effectiveness ratio of HER2-testing becomes less favourable. Changes in quality of life leads to comparable results: if the quality of life was assumed to be lower in women treated with trastuzumab compared to women that are not, the cost-effectiveness ratio becomes less favourable. Also if the quality of life in women treated with trastuzumab and the women treated with chemotherapy alone, were lowered simultaneously, the cost per QALY gained becomes higher (i.e. a less favourable cost-effectiveness ratio).

In a probabilistic multivariate sensitivity analysis we assumed a uniform distribution for the parameters between the lower and upper value presented in Table 8.

In varying the model parameters together we assumed that the median survival of women treated with chemotherapy and trastuzumab could not be lower than the median survival of women treated with chemotherapy alone.

In this way we estimated that with a probability of 62% strategy 3 (use FISH as confirmation of all positive IHC results) has the most favourable cost-effectiveness ratio (lowest costs per QALY gained).

With a probability of 32% strategy 5 (use FISH alone) is most favourable, and with a probability of 6% strategy 1 (use IHC with 3+ as cut-off-point) is expected to yield the lowest costs per QALY gained.

The most important parameters determining the variance in cost-effectiveness are the median survival estimates, the additional costs of treatment with chemotherapy and trastuzumab compared to chemotherapy alone, and the quality of life of women with metastatic breast cancer.

2.6 Discussion

Pharmacogenomic treatment strategies offer the potential to improve drug effectiveness, reduce adverse drug reactions and provide cost-effective care. However, pharmacogenomics has had little impact on clinical practice. This may be due to medical, social, ethical, and financial barriers. Information on cost and effects of pharmacogenomic treatment strategies provided by cost-effectiveness analyses may level (part of these) barriers.

Although an increasing number of applications of pharmacogenomics are described in literature, the economic implications of pharmacogenomics are less often studied. In a recent systematic review of cost-effectiveness analyses of pharmacogenomic interventions Phillips & Van Bebber (2004) identified only 11 studies that met the inclusion criteria for a cost-effectiveness analysis. In this study two examples of pharmacogenetic testing are analysed: HER2-testing (efficacy of trastuzumab) in women with metastatic breast cancer and TPMT testing (safety of thiopurine drugs) in children with ALL.

For both applications an explorative cost-effectiveness review was performed by developing models for the comparison of the costs and effects of the pharmacogenomic treatment strategy with the current medical practice. For the four participating countries (Germany, Ireland, United Kingdom and The Netherlands), information on model parameters was collected from literature and expert opinions.

The explorative analysis on TPMT testing in children with ALL revealed an expected cost-effectiveness rate of € 4,760 per life year gained (3% discounting). Phillips and Bebber (2004) assume an intervention to be favourable if the cost-effectiveness rate is lower than US\$ 50,000. Our base case estimate for TPMT testing in children with ALL compares favourable with this threshold.

In the sensitivity analysis, it was established that the maximum cost per life year gained, given the range of parameter values that seems plausible, are € 101,240, but TPMT could also lead to both financial savings and a gain in life years.

For a more definitive estimate of the cost-effectiveness of TPMT testing in children with ALL, further research on the costs of the PCR test and the mortality prevented by TPMT screening has a high priority, as these model parameters had the most important influence on the variance in cost-effectiveness.

Our analysis on HER2 testing in women with metastatic breast cancer shows that the use of the FISH test as confirmation of all positive IHC results and the use of the FISH test alone are efficient strategies. This is in accordance with the study of Elkin et al. (2004). These results are confirmed in the sensitivity analysis.

Given the range of model parameter values that seems plausible, only with a small probability (6%) the use of the IHC test alone, with 3+ as cut-off-point, is expected to yield the lowest costs per QALY gained.

The costs per QALY gained, however, are relatively high for the efficient strategies. The incremental cost-effectiveness ratio is expected to be € 90,500 per QALY gained for the use of the FISH test as confirmation of all positive IHC results compared to no testing, and € 95,200 per QALY gained for FISH alone compared with IHC testing followed by FISH confirmation of 2+ and 3+ results. The median survival of women with metastatic breast cancer for the different treatment strategies, the additional costs of trastuzumab and the quality of life of women with metastatic breast cancer are the parameters that has a high priority in further research on the cost-effectiveness of HER2 testing in women with metastatic breast cancer.

There are a number of limitations to this study. Models are always a simplification of reality. Sometimes, the abstraction made in this study is quite rough due to the time-frame of this study, and more sophisticated models may be more appropriate to obtain estimates on the cost-effectiveness. However, our results on the cost-effectiveness HER2-testing were in accordance with the results of a more sophisticated model on this subject (Elkin et al. 2004). Except for this model uncertainty, the study is also subjected to parameter uncertainty. The model parameters are based on literature review and expert opinions. Part of the information was not available for the participating countries, and estimates for model parameters for another situation derived from literature review were used. For the TPMT study even hardly any information was available specifically for children with ALL. Therefore, estimates from pharmacoeconomic studies on other thiopurine drugs are frequently used. Part of estimates for the model parameters is based on expert information. Although this is valuable for an explorative study, there is no uniform method of assessing an estimate. The reported differences between estimates in costs between countries may therefore reflect real differences between countries, but also cost components included and estimation methods may differ. To explore the role of parameter uncertainty, sensitivity analyses are performed, in which the influence of changes in the model parameters is investigated. In this way, it can be inferred how the cost-effectiveness estimate will change, if further research for a model parameter will

show that this estimate is different from the estimate used in the base case analyses. Further research on model parameters, preferably in a prospective study using a standardized method is warranted, especially for the TPMT model.

In conclusion, this exploratory study has provided information on the expected cost-effectiveness of HER2 testing in women with metastatic breast cancer and TPMT testing in children with ALL, and identified the parameters that need to be estimated more accurately to give a more definitive estimate of the cost-effectiveness of both pharmacogenomic strategies.

This kind of explorative study combining available evidence from literature with expert opinions is useful for prioritising cost-effectiveness research on pharmacogenomic strategies, and identifying which model parameters should be included in further research on the cost-effectiveness of this pharmacogenomic strategy, preferably in a prospective study using standardized methods.

2.7 Conclusions

- Clarifying the economic implications of pharmacogenomic treatment strategies is important, as this may facilitate the implementation of pharmacogenomic treatment strategies
- Cost-effectiveness analyses of applications of pharmacogenomics are sparse
- Scarce data available for studying the cost-effectiveness of TPMT testing (safety of thiopurine drugs) in children with acute lymphoblastic leukaemia
- Large differences in costs reported between countries
- TPMT test has a favourable cost-effectiveness ratio
- FISH alone or FISH as confirmative test after an IHC positive result are preferable strategies for HER 2 testing

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3. Case studies: HER2

3.1 Germany

3.1.1 Introduction of HER2-test and Herceptin® in Germany

In 1982 a research group around R.A. Weinberg at the MIT in Boston discovered along with other experiments the HER2/neu gene.¹ A. Ullrich cloned the gene in California in 1984. Shortly after, D. Slamon conducted the first epidemiological studies with breast cancers. The next historical milestone in the history of Herceptin® was the discovery of a humanized antibody by Paul Carter and Len Presta from Genentech in 1990. One year later, phase I trials were initiated. In September 1998, Herceptin® was approved by the US Food and Drug Administration (FDA) for the treatment of women with HER2 positive metastatic breast cancer, both as first-line therapy in combination with paclitaxel and as a single agent in second- and third-line therapy. For distribution of the drug outside the United States, Genentech and Roche signed a licensing agreement giving Roche exclusive marketing rights. The first country introducing HER2-testing in Europe was Switzerland. It was introduced there in 1999.

Germany followed soon after in the year 2000. Herceptin, being a monoclonal antibody, was approved via the centralized European procedure. Germany (Paul-Ehrlich Institute) and Denmark served as reference countries (rapporteur) and were therefore the first countries within Europe that applied Herceptin in clinical settings. According to Roche, two studies including eight different centres in Germany alone were involved in pre-approval studies for the use of Herceptin in combination with taxol (first line) and as mono-therapy (further line). To grant adequate access (within 24 hours) for the hospitals to the drug during clinical studies, the Suisse government agreed to establish duty free storage of the drug within its borders.

The approval process went without any disturbances. There were no problems due to the fact that the authorities dealt with a drug-test combination. As the DAKO-test was already on the market and proved adequate within the initial clinical trials to predict response, no hindrances arose. According to the initial approval documents Herceptin could only be prescribed to HER-positive women (score 2+ and 3+) according to an immunohistochemical test. This state applied to around 25-30 per cent of all breast-cancer patients. Since October 2004, this has changed regarding the realization that the application of Herceptin does not make sense for all women being HER-positive at a score of 2+. To further evaluate whether the prescription of Herceptin makes sense, another test was introduced, the fluorescence in-situ hybridisation (FISH) test. To establish FISH testing in Germany, Roche approached five pathological centres throughout Germany and tried to gain them as reference centres for re-testing of probes with FISH. This campaign already started in the year 2001.

¹ Elling (2003), p. 110.

These five centres still serve as reference centres, despite the official validation of FISH testing for HER2 status. Roche itself now estimates the number of patients that potentially benefit from the drug of around 20-25 per cent. (Whereas doctors say that it must be even less- around 10 to 20 per cent at most.)

As eight different centres were involved in the approval process several doctors were already familiar with the product test combination at the state of actual approval. Since then, around one hundred different centres within Germany were involved in different studies including Herceptin®.

According to experts' opinion, the marketing of the drug was immense. It was a theme in all sorts of magazines which led to the astonishing circumstance that affected women already knew the drug before treatment and even now claim a HER2 test as they read about it. Also the width of the actually conducted HERA study to introduce Herceptin as a therapy in the early states of breast cancer over flooded the market with 87 centres involved in Germany alone. This study is ample known.

3.1.2 HER2-test and clinical practice

Immunohistochemical HER2 testing is now in most hospitals an integral part of routine laboratory testing of tumour tissue. In the words of one physician: "Every good institution does it". Two certified test kits for the detection of HER2 status via immunohistochemistry exist on the market that differ with respect to the antibodies used:

- the HercepTest by DAKOCytomation and
- the CB11 antibodies produced by Ventana.

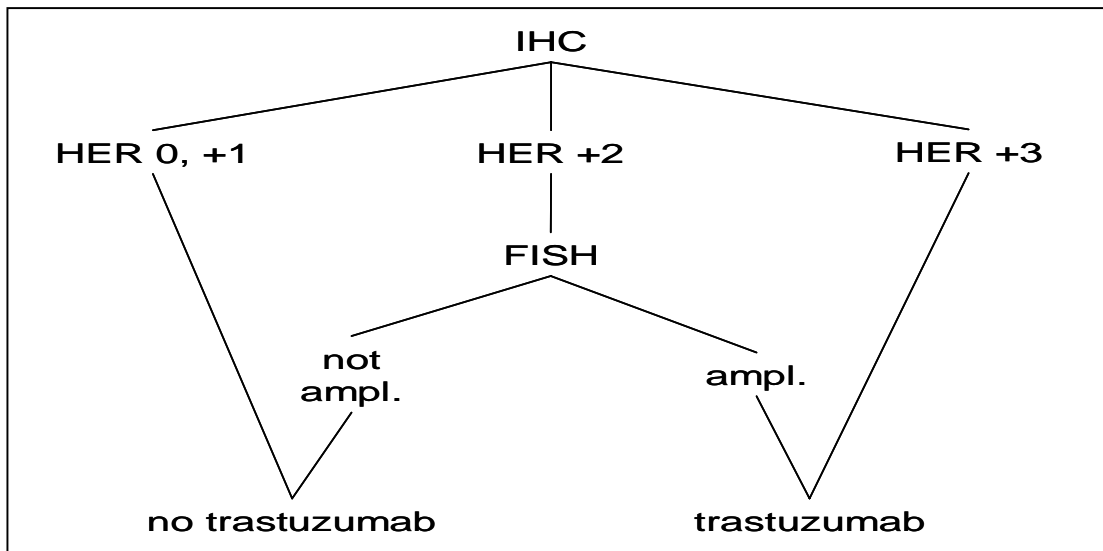
As described above, Roche gained five well known pathological centres throughout Germany as reference centres for re-testing of probes with FISH. Regarding the rare incidence of HER2 score 2+ cases as well as the high cost and additional knowledge needed to conduct the FISH test, clinics still send the probes in question to these specialized pathologists of high reputation to evaluate the probes using the FISH technique.

Both methods –IHC and FISH- have advantages and shortcomings. Advantages of IHC staining include its wide availability, relatively low costs and times, easy preservation of stained slides and use of a familiar routine microscope. But there often occur wrong evaluations of the probes. The test is stated not to be highly sensitive and great expertise is needed to evaluate the probes correctly. Contrarily to this more or less qualitative evaluation, the FISH technique can be automated and has a more objective scoring system. Its only shortcomings are the costs of each test, the longer time required for the test results and the additional knowledge needed. The FISH procedure takes up to ten days until the results are sent back- compared to IHC staining which can be done in 3 to 4 days.

To make HER2/neu diagnosis as valid as possible and also as practicable and cheap as possible, experts of a designed pathology board have agreed upon the following algorithm for testing which is mapped below.²

² Elling (2003)

Figure 2 Algorithm for HER2 testing



Source: Elling (2003)

Summing up, FISH is stated to be more sensitive, but too expensive, apart from the additional expertise needed. To solve this problem, new techniques are being invented that facilitate the technique. With new methods such as rqPCR, economies of scale and scope could potentially be achieved.³ Whether this makes sense regarding the rare incidence of cases is questionable and maybe depending on the results of further studies, such as HERA, with the aim of intensifying the use of the drug and turning it to a standard procedure also in other fields.

The pros and cons of Herceptin® itself are controversially discussed among physicians in Germany. The main hindrance is the perceived cost benefit ratio. Herceptin® is seen as a much too expensive treatment keeping in mind that it provides no cure, but can only extend the length of a patient's life for a few more months. In this sense also the actual application method is criticized. Herceptin® is currently applied via infusions once a week which represents an impairment of the patient's quality of life and it is accompanied with other, in part severe, side affects. Especially due to the high costs, Herceptin® wasn't regularly prescribed in the interviewed hospital.

As mentioned before, the perceived actual number of cases in which Herceptin® could be prescribed is at a much lower level than reported in studies and amounts to a total of maximum 20 per cent. The next fact is that not all women diagnosed as HER2 positive automatically receive the treatment with trastuzumab. The test can also serve as a mere means to forecast the probable development of the cancer.

³ Lewis et al. (2004)

HER-2/neu receptor status is now routinely measured in every mammary carcinoma in the majority of German hospitals, at least via immunohistochemical staining. With every tumour probe, there's a whole range of tests being conducted and also due to the fact that a common microscope can be used, no big organisational adjustments had to be undertaken. As stated, the FISH test as supplementary measure in the case of a score of 2+ is being conducted in specialized centres. As there are only very few ones in Germany, the procedure, consisting of sending the probe away, testing and getting back the result, was said to take up to ten days. Still, according to interviewees, this doesn't happen very often.

Herceptin is currently applied as well as a mono therapy as in combination with chemotherapy. Regarding current trends in the application of trastuzumab we got some interesting insights:

Concerning additional costs occurring because of the application of Herceptin, one issue has to be mentioned, concerning the way, trastuzumab is applied. The antibody is applied via infusion. This procedure consumes not only resources for the medication itself but also material costs for the transfusion and time costs on the side of the hospital staff and on the part of the individual patient who has to come back to the hospital once a week. The infusion itself was reported to take around 90 minutes for the initial infusion and then regularly around half an hour. One might as well include a waiting period for the individual patient that was reported to vary between one and two hours. According to experts, Herceptin could also be given once every three weeks at a dose of 6 mg/kg as the serum level was said to remain the same. The half-life period was said to have been underestimated initially. Given the mentioned critique of diminished quality of life for the patient due to the actual application method, this offers a great chance.

As one physician stated, Herceptin is mostly (in around 80 % of the cases) given at first in combination with a chemotherapy and later on, if chemo failed, as mono therapy. If no response is seen, treatment with these antibodies will be stopped. In all other cases, Herceptin is at least given until disease progression if not even longer (depending mainly on the willingness of the respective insurance company to pay). It is not yet clear, whether and for how long trastuzumab therapy should be continued and whether treatment with trastuzumab should even be continued after progression which is contrary to the current official information for doctors. The reason for this is simple: as it is not yet ensured whether, after the withdrawal of trastuzumab, signal transduction will come back or not, it makes more sense to continue the treatment. In case of a revival of the signal transduction, further chemotherapies would be put into question.

To prove this, further studies that aim at proving the sense of continuing trastuzumab chemotherapy even after progression of the disease state are being conducted. One example is the current study by Dr. Minckwitz in Frankfurt who compares the effect of capecitabin (Xeloda®) given alone or in combination with trastuzumab after progression given a pre-treatment with trastuzumab. Herceptin's future success will also depend on further studies that concentrate on alternative applications of the anti-body. Currently, twelve different studies were found to be conducted in Germany that are briefly outlined in the table below (table 12).

Table 12 *Current studies regarding the use of Herceptin*

<i>study</i>	<i>short description</i>	<i>scope (number of centres involved)</i>
Herceptin, study 1	combination therapy of Herceptin® (trastuzumab) and Anastrozol (arimidex)	6
Herceptin, study 2	combination therapy of Herceptin® and docetaxel (administered in different intervals)	50
Herceptin, study 3	combination therapy of Herceptin® and epirubicin	30
Herceptin, study 4	mono therapy of Herceptin (3 weekly administrations)	2
Herceptin, study 5	combination therapy of Herceptin® and vinorelbine (Navelbine)	3
Herceptin adjuvant (HERA study)	Within the HERA study, HER2 anti-body is to be tested in a very early stage	87
Herceptin, study 7	Pre-operative (neo adjuvant) therapy before operation, in which Herceptin is administered together with a taxane, after antecedent therapy with epirubicin. Subsequently, an operation takes place, followed again by an after-treatment with Herceptin for further 9 months	30
Herceptin, study 8	Before operation (so-called pre operative protocol), HER2-positive patients are administered epirubicin and cyclophosphamid followed by taxol/Herceptin. After operation, treatment with Herceptin is continued for another 36 weeks	30
Herceptin ("Fakt-Studie")	therapy with Herceptin and taxol; study is being conducted by a settled oncologist	1
Herceptin ("MammaHER2")	multi-central treatment study with Herceptin	
Herceptin and xeloda	combination therapy of the oral cytostatic xeloda and the anti-body Herceptin	
Herceptin and navelbine	combination therapy of the cytostatic navelbine in connection with the anti-body Herceptin	

Source: Mammazone

One study is worth going further into detail: Already in 2001, a randomized, two-arm, open label study of the efficacy, safety, and tolerability of Herceptin when given after standard chemotherapy in women with early stage breast cancer called HERA

(Herceptin® Adjuvant Trial) study, has been launched. The study is a world-wide study that is being coordinated by BIG (Breast International Group) and Hoffmann-La Roche Ltd. Approximately 5,100 patients from 480 centres world-wide in 39 countries are involved. Within Germany, 87 centres take part, which represents the largest study conducted in this field. Initial recruitment of patients for the HERA trial began in December 2001. Meanwhile, recruitment of patients was stopped and first mid-term evaluations actually revealed a reduction of 52 % in the risk of developing the tumour again and a reduction of 33 % in the risk of death.⁴ Yet, the final results are not expected before the year 2006. This example shows the immense efforts on the side of Hoffmann-La Roche to extend and intensify the use of the monoclonal anti-body trastuzumab. Roche itself is convinced that targeted medicine is the right approach for future research in terms of avoiding unnecessary therapies under ethical and financial aspects. In oncology, they've recently got the approval for their third targeted antibody bevacizumab (Avastin®) for the treatment of metastatic colorectal cancer.

3.1.3 *Quality aspects*

In Germany, immunohistochemical tests are either conducted in a clinical pharmacology or in an external laboratory whereas FISH testing is conducted in specialized centres. Within the interviews it was discovered that the results gained in both settings vary in respect to quality assurance and the proceeded report. Whereas most commercial laboratories tend to follow the voluntary accreditation system, most internal (hospital) labs are not accredited as there exists neither a compulsory certification for products such as PGx tests used in-house nor a compulsory accreditation system for labs.

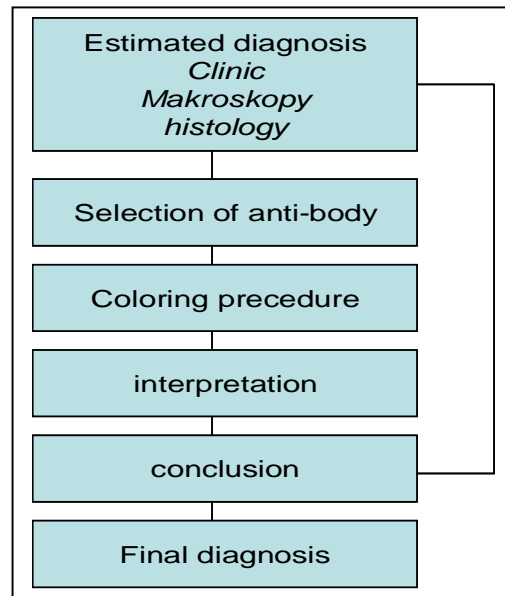
According to interviewees medicinal laboratories follow accreditation systems for marketing reasons though smaller laboratories hesitate due to the high costs and bureaucratic and time consuming procedure. Commercial providers of diagnostic testing services have to assess the quality of their offered services regularly. § 135 a SGB V dictates internal and external quality assessments in German hospitals, yet, this regulation was seen as too broad to have actual consequences.

In Germany, the use of officially approved test kits is not binding. The approval documents just claim the accomplishment of a test in general. As the official test kits are claimed to be very expensive, laboratories rather try to avoid their use. One laboratory reported the proceeding that only antibodies that bind the receptors are procured from official certified producers, whereas the rest, namely the colouring antibodies, are “home-brew”. They claimed that they’d “go bankrupt” if they used the whole test kit. According to internal estimations by DAKOCytomation, the market share of procured complete test kits must amount to only around 20 to 25 %. Regarding these home-brews, unified certification standards would be necessary.

⁴ <http://www.presseportal.ch/de/print.htx?nr=100490174>.

Yet, it was hard to evaluate the quality of a lab in the field of immunohistochemistry. The following steps have been identified as crucial:

Figure 3 Single steps of clinical immunohistochemistry



Source: Rüdiger et al. (2003)

The only means to approach real processes as close as possible is to conduct ring studies that include different steps of the process. Yet, the participation at ring studies is still on a voluntary basis. This was partially approved of by laboratory physicians, as each quality measure is accompanied by additional (bureaucratic) work, and represents a financial burden; although they are aware of the problem.

Roche itself sees this problem and criticises this common procedure (“The test quality represents an absolute critical theme”) as well as approval authorities who claim that their “hands are tight”. Only those hospitals taking part at clinical trials are obliged to show their certification. It was generally noticed that the number of tests conducted and the quality of results are positively correlated. Therefore, the number of tests conducted is more or less reliable quality indicator. Interviewed laboratory physicians also assumed there would probably be more pressure exerted on them in the future.

3.1.4 Approval and reimbursement

PGx applications consist of a pharmaceutical/diagnostic test combination. Prerequisite to grant save applications in this new field is an effective approval process. So far, no pharmacogenetic specific process for approval has been designed in Germany. At present two different bodies of authority are responsible both for the approval of pharmaceuticals and the validation of medical devices.

Apart from some specific exceptions that belong to the scope of responsibility of the PEI, the approval process of pharmaceuticals and the validation of medical devices are incumbent on the BfArM. The PEI is responsible for the approval of immune-biological pharmaceuticals, such as serums, vaccines, blood products, test allergens, test sera and test antigens as well as the validation of in vitro diagnostics. With the conversion of the EU in-vitro diagnostic directive into German law in the course of the German "Medizinproduktegesetz" (law on medical devices), a new testing laboratory has been established within the PEI, the so-called PEI-IVD. Since the end of the year 2003, this especially dedicated laboratory cooperates with other 'notified bodies' in the field of in-vitro diagnostics.

The declared way for test/pharmaceutical combinations is to stick to the German two-track proceeding of approving pharmaceuticals and validating medical devices by separate authorities: An officially validated test has to exist that proves efficient before the respective pharmaceutical can enter the market. This will be evaluated by the authority in the approval process within the evaluation of the effectiveness of the new drug. As for the detection of HER2 overexpression such a test was available, Roche had no problems in getting market approval.

A crucial point linked to the high costs of the product is the current situation of reimbursement. In Germany, three different bodies of rules are relevant regarding PGx applications: the so-called EBM ("Einheitlicher Bewertungsmaßstab") that applies for the settled and out-patient sector in the case of statutory insurance membership, the GOÄ ("Gebührenordnung für Ärzte") that defines the reimbursed sums for out-patient treatment and in-patient services for privately insured and other groups such as civil servants and the newly introduced DRG (Diagnose Related Groups) list for statutory in-patient care, respectively.

Within the first two bodies of rules, trastuzumab and immunohistochemical staining can be cleared. According to one interviewee from a hospital pathology, there's one limitation to this. Subject to applicable law, only three different anti-bodies are being reimbursed within the GOÄ. It is up to the laboratory expert to choose the appropriate ones among a variety of possibilities. This is a source for potential quality problems as was realized within the interviews. One ring study conducted in the year 2000 revealed grave problems regarding the choice of appropriate anti-bodies as was described in chapter 5. Within the DRG system, the appropriate category for breast cancer into which the treatment has to be classified in general is J62 ("malignant growth of mamma").

Depending on the occurrence of complications, different sub-categories exist. To compensate higher costs through the application of high-price innovative treatments an additional catalogue has been drafted. Trastuzumab is part of this catalogue and the costs of the medication can therefore be cleared separately. It seems that this regulation is not yet a common fact among doctors as one interviewed physician claimed that Herceptin could never be afforded within the provided means for the treatment of breast cancer.

A better education of physicians in this respect and a better communication between the attending physician as well as the laboratory physician and the accounting centre were claimed to prevent these misunderstandings. But there's one more hitch to this regulation: the sum of these additionally reimbursed treatments per hospital may not exceed the sum total of 10 per cent of the whole hospital budget. This again could lead to financing problems of the drug.

Regarding the FISH technique, it is still Roche carrying the costs even after official approval of the test in November 2004. This procedure has to be seen against the background of the reimbursement system. It is up to the Federal Joint Committee (G-BA) ("Bundesausschuss der Ärzte und Krankenkassen") to decide upon the future reimbursement of a pharmaceutical or medical device, respectively. Common procedure to route or influence this process is to diffuse the innovation ex ante among doctors and to gain patients' trust. Combined with the competitive situation among insurance companies, a positive outcome of the decision process is being anticipated.

It was further observed that patients are consistently willing to raise own money within the scope of their capabilities to have access to a drug that might help them. Yet, physicians often think within general applied patterns and sometimes don't even offer this possibility to the patient who herself does not dispose over an overview of the possibilities.

3.1.5 Economic aspects

Breast cancer represents the most common cancer disease in women.⁵ In the year 2000, 47,517 new incidences of breast cancer occurred and 44,860 cases were reported that occurred for the very first time. Statistically, about 40% of these patients have metastatic disease, which are around 19,000 patients in Germany alone.

Only a rare number of economical evaluations of Herceptin® exist. In Germany, there exists only one official "opinion on the use of the antitumour drug trastuzumab in patients with metastatic breast cancer", dating from the year 2001. In this statement, trastuzumab at a total treatment cost of 48,000 DM (24,500 €) was seen as expensive, regarding the fact that it does not provide a cure of the disease, but only prolongs survival. Because of a high observed incidence of adverse events (cardiac dysfunction NYHA III or IV in 27 % of the group given an anthracycline, cyclophosphamide, and trastuzumab) they came to the following result: "In patients with moderate HER-2/neu expression, unwanted drug effects outweigh the relatively low therapeutic benefit. In cases of high over expression, cancer regresses and survival is prolonged with a slight impairment in the quality of life."⁶ Their recommendation for economical prescribing is therefore to only prescribe trastuzumab to patients with a score of 3+. Yet, this was before the wide introduction of FISH testing.

This result corresponds to the physicians' perceived cost-effectiveness ratio. Compared to the additional costs and the additional burden on the part of the patient, costs of the medicine are perceived as being too high which prevents doctors partially from prescribing the drug. In view of newer trends to apply a higher dosage once every three

⁵ Robert-Koch-Institut (2004).

⁶ Hehl, E.-M. (2001), p. 505.

weeks, vide chapter 2, not only stress can be reduced but also medical material accumulated with the time can be saved.

Yet, side effects also represent a problem. Reported side effects in the short-run are toxic effects that occur in about 30 to 40 per cent of treated patients. These side effects are said to be of minor importance as they don't need any additional treatment and would diminish after the first few sessions. In the long-term consideration, two severe side effects are mentioned: infusion associated anaphylactic reactions and the occurrence of heart insufficiencies in around 5 to 10 per cent of cases. Patients suffering from heart insufficiencies were in the majority of cases pre-treated with anthracyclines. In all other cases the incidence rate is reported to be smaller. To prevent heart insufficiencies, regular heart ultra sound measurements are conducted that claim additional resources. These measurements are conducted every three months. In case of a treatment with trastuzumab until progression during a time period of 19 months, this has to be done seven times. If heart insufficiencies actually do occur, treatment with trastuzumab is stopped and routine treatment methods such as ACE-inhibitors, diuretics are being applied.

3.1.6 Societal aspects: patients' attitudes

The monoclonal anti-body trastuzumab, more common under its trade name Herceptin®, is widely known. The distinctive difference compared to the poorer spreading of TPMT testing is primarily the interest of a huge pharmaceutical company promoting the product in the case of Herceptin, where newspaper articles, also in the popular press, and latest news on the HERA study swept the country during the last couple of years.

The drug seems to have been marketed in a very pushy pattern. As one pathologist stated:

"Women call me and have three different claims:

1. Breast conserving surgery,
2. Removal only of the sentinel node and
3. Herceptin.

Roche did a real good job."

This forces physicians indirectly to test HER-2/neu status of the patient, even contrary to own doubts regarding the effectiveness of the drug.

It was reported that women, especially at this stage of disease progression, would do anything that might help to at least prolong their life-expectancy for a few more months.

Regarding the potential benefits that can be derived from pharmacogenetic applications for patients, there was a clear consensus among the questioned parties. Whereas in the case of TPMT, the safety of medicines in terms of an avoidance of adverse reactions is in the foreground, Herceptin was the first target-specific medication on the market. To sort out patients that won't profit from the medication ex ante is clearly approved as every medication is accompanied by side effects. Not to burden patients with additional stress that is unnecessary and to raise hopes that can't be fulfilled was consistently seen as positive.

Regarding future applications, the only concern is that patients that show only a marginal chance that the drug might help -as we are talking about mere probabilities- won't have access to the drug at all. This is a critical issue that is not yet solved.

Worth mentioning again in this respect is the reported fact that patients would always be willing to contribute financially in case a medication exists, within their personal

constraints, of course. Critique was being expressed, that doctors are sometimes focused on standard patterns and don't tell the patient that there might be another possibility that is not (completely) being reimbursed. This plea should be directed versus doctors.

Several ethical or societal problems that might occur in the course of introducing pharmacogenetic methods were being discussed, among them data protection problems, a potential elevation of supplementary information and how to deal with it in the case of occurrence, as well as information on disease predisposition regarding other family members. Whereas in other constellations, the problem of retrieving additional information was seen as a future problem and also concerns for other family members were forwarded, this was not of great importance within the Herceptin case. But also knowledge on the probable development of the disease can be seen as supplementary information. As HER2 overexpression is linked with a bad prognosis of the disease progression, this information can also weigh heavily on the patient. Regarding Herceptin, hereditary concerns do not occur, as no germ line polymorphisms are regarded, but a somatic mutation. This situation changes when looking at for example BRCA1, BRCA2 mutations that are hereditary. Therefore, no special informed consent and education process have been designed. HER2 testing is part of a whole range of tests being conducted.

Summing up, Herceptin is seen as a quite expensive medication that does not provide complete cure, but prolongs life for a few more months. Still, it has proven to be effective and is already widely applied on the market. Its future success certainly depends on future studies that are on the way.

Interviews:

2 Research Laboratories (Pathological Institute, University Würzburg; University Clinic Würzburg)

3 Clinical Laboratories (Breast Centre Heidelberg; Institute of Pathology, University Clinic Kassel; Gynaecological Department at the Medical Mission Institute Würzburg)

3 Officials of Sickness Funds (Münchner Rück; Hamburg Münchner Krankenkasse, DKV Köln)

3 Company representatives (Hoffman-La-Roche, DAKOCytomation, Verband der forschenden Arzneimittelhersteller (= German Association of Research Based Pharmaceutical Companies))

2 Officials from the Medicines and Healthcare Products Regulatory Agency (PEI, BfArM)

2 Representatives of Patient Organisations (Cancer Association Baden-Wuerttemberg, Cancer Association of Berlin)

1 Official of the German Parliament

1 Official of an ethic commission

1 Official of the Central Authority of the Laender for Health Protection Regarding Medicinal Products and Medical Devices

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3.2 Ireland

3.2.1 Introduction of HER-2 test and Herceptin in Ireland

Following on the development and EMEA approval of Herceptin in the USA and in certain EU countries, an application by Roche Registration Limited for Herceptin use in Ireland was approved by the Irish Medicines Board (IMB) (Licence Number EU/1/00/145/001) in September 2000. The specific formulation is HERCEPTIN 150MG (cost € 950 per 150 mg). 1 vial contains 150 mg of trastuzumab, a humanised IgG1 monoclonal antibody manufactured from a mammalian cell line (Chinese hamster ovary, CHO) by continuous perfusion. Reconstituted Herceptin solution contains 21 mg/ml of trastuzumab.⁷

According to the conditions of approval by the Irish Medicines Board, Herceptin could only be prescribed to patients who had been shown to be HER-positive by using an 'accurate and validated assay'.

Effectively the sole supplier of this assay is DakoCytomation, which supplies two HER2 testing kits in Ireland:

- HercepTest™ was the first FDA-approved diagnostic kit designed to quickly and accurately identify patients eligible for Herceptin™ therapy.
- HER2 FISH pharmDx™ Kit is the second HER2 diagnostic kit indicated as an aid in the assessment of patients for whom Herceptin™ treatment is considered. This latter test is not approved for use in the USA or Japan. This has only been introduced recently and as yet the cost has not been fully calculated. It is more

⁷ Data from Roche website: www.rocheuk.com/ProductDB/Documents/rx/pil/Herceptin_PIL.pdf

expensive than HercepTest and the price charged will probably be in the region of €250 per test

Both tests are CE marked and in use for diagnosis of Breast cancer.

HercepTest was introduced into Ireland in 2000 and is supplied free of charge to user laboratories as part of Roche's programme to promote the use of Herceptin. The company provides significant support to users laboratory staff, and to physicians using Herceptin, in the form of information, training and on-going help-line and web-based information.

Both of the above Her2 kits are also used in other cancers (where Her-2 is expressed) as a research tool. There have also been several papers published by Irish clinical research groups on alternative approaches to HER2 testing, and also to simpler methods for taking samples prior to FISH testing.⁸

According to DakoCytomation (Ireland), Herceptest is used in all the teaching hospitals. These kits are supplied to user laboratories at no cost by arrangement with Roche (Ireland). The FISH test is also used but the main centre for its use is Tallaght Hospital.

Although it is available, DakoCytomation (Ireland), are not aware of any pathology laboratory in Ireland using the Chromogenic *in situ* hybridization (CISH) assay. There are very stringent protocols for performing the assays and there is continuous training and support provided by DakoCytomation.

Breast cancer is the most common cancer in women in Ireland (after non-melanoma skin cancer). According to 1996 data from the National Cancer Registry⁹, the risk to a woman of developing breast cancer before age 75 years is 7.9% and the risk of dying of breast cancer before age 75 is 2.8%. The mortality/incidence ratio is 38%. Approximately 1,670 women were diagnosed with breast cancer each year from 1994 to 1996 and 650 women died from the disease.

Further data in 2000 shows that the incidence from 1994 to 2000 was 1,683 diagnoses per year. This mortality rate is higher than the European average, with only Denmark and the Netherlands ranking higher than Ireland. 1 in 14 Irish women will develop a breast cancer malignancy. It is rare in women under thirty and occurs most frequently in later life.

Figure 4 Annual Episodes of New cases of Breast Cancer

1994	1995	1996	1997	1998	1999	2000	2001	2002
						*	*	*

⁸ See references Gulmann et al (2004); Kay et al (2004); and O'Grady et al (2003)

⁹ Cancer in Ireland, 1996. Incidence and Mortality. Report of the National Cancer Registry. September 1999.

All Cancers	9679	9429	10008	10231	10215	10342	10610	10836	11077
Female	1505	1525	1588	1614	1689	1738	1793	1856	1921
Male	13	8	17	16	10	14	14	15	15
Total	1518	1533	1605	1630	1699	1752	1807	1871	1936

3.2.2 HER2 test and clinical practice

HER2 is now a standard test used in all hospitals and clinics involved in breast cancer therapy and is conducted on virtually all patients presenting with breast cancer. The forms of treatment of breast cancer have been varied (see below) but chemotherapy has gradually become more common as more effective drugs appear. From 1994-97 approximately 40% of cases were treated by chemotherapy, while in 1998-2000 this had risen to 45%.

Figure 5 Main inpatient procedures for breast cancer; 1994-1999 averages

Table 11. Main inpatient procedures for breast cancer; 1994-1999 averages		Episodes	% of total
Operative procedures		1188	49%
Unilateral extended simple mastectomy		504	45%
Local excision of lesion of breast		238	19%
Unilateral simple mastectomy		180	9%
Subtotal mastectomy		134	7%
Unilateral radical mastectomy		59	5%
Resection of quadrant of breast		58	2%
Unilateral extended radical mastectomy		8	2%
Bilateral simple mastectomy		2	<1%
Bilateral extended simple mastectomy		2	<1%
Other surgery		4	1%
Non-operative procedures		936	39%
Teleroadiotherapy		242	10%
Injection or infusion of cancer chemotherapeutic substance		236	10%
Needle biopsy of breast		74	3%
Open biopsy of breast		57	2%
Bone scan		20	1%
Transfusion of packed cells		17	1%
Diagnostic ultrasound of abdomen and retroperitoneum		16	1%
Injection or infusion of other therapeutic or prophylactic substance		16	1%
Computerised axial tomography of head		15	1%
Thoracentesis		14	1%
Excision of axillary lymph node		14	1%
Injection of antibiotic		12	<1%
Transfusion of whole blood		10	<1%
Other non-operative procedure		194	8%
No procedure recorded		295	12%
Total		2419	

Although Her 2 testing is now standard, Herceptin is not widely used. To illustrate this, the clinical guidelines for Breast cancer (Jan '04) in one major hospital in Ireland (Cork University Hospital) consider Herceptin useful only in Stage IV metastatic disease.

Figure 6 Preferred chemotherapy regimens for metastatic disease

Preferred first-line chemotherapy
Anthracycline-based, taxane* or CMF
Preferred second-line chemotherapy
If first-line was anthracycline-based or CMF, then taxane*
If first-line was taxane, then anthracycline-based or CMF
Other active regimens include vinorelbine, infusion 5-FU, capecitabine, mitoxantrone, & mitomycin-c
*In patients whose tumour overexpresses HER-2/ <i>neu</i> , consideration may be given to using trastuzumab in combination with paclitaxel. Trastuzumab has also been given in combination with AC, but the use of trastuzumab plus AC is associated with significant cardiac toxicity.

The extent of use of Herceptin is further discussed in the section below.

In regard to the use of HER2 testing, it is useful to note the background to clinical testing. Irish hospitals have historically had their own in-house analytical laboratories and there is currently no move to centralize such testing. Cancer therapy is, however, centralized within certain hospitals and therefore specialized testing such as HER2 will only be of relevance to laboratories within these specific hospitals. Thus laboratories are only dealing with small numbers of HER 2 testing samples. However, these hospitals may sub-contract certain low-volume tests to a particular hospital. This has been the case in HER2, where the Dublin hospitals have centralized testing in Tallaght General Hospital.

Some of the national centres for HER 2 testing are therefore the Tallaght General Hospital (which provides testing for most Dublin hospitals), Cork University Hospital and Galway University Hospital. In another major hospital – St. Vincent's Hospital, Dublin, there are approx. 200 Her2 tests per annum. These are histochemical in nature, and are routinely requested by medical oncologists.¹⁰

The major Irish centres also use the FISH test and there seems to be a preference for the latter as being less subjective than the HER2 test. One interviewee also noted that the FISH test was preferred because it allows assessment of the effects of the treatment on gene expression. There has also been active research to develop easier sampling methods, using fine-needle aspirates, for tumour samples prior to using the FISH test.¹¹

On the general use of PGx tests, it was noted that the newer consultants being appointed are far more comfortable with the concept of genetic testing than the older consultants. The fact that there have been several new appointments in the Irish health system was helping the process of introduction of these tests.

The Irish Clinical Oncology Research Group was established in October 1996 to facilitate clinical trials and other research in oncology. It is composed of specialists working in the

¹⁰ Interview with clinical biochemist consultant

¹¹ Mc Manus et al (1999)

oncology field in the Irish Republic and Northern Ireland, who have the common goal of increasing the level of clinical cancer research in Ireland.¹² They are currently running 2 clinical trials in which patients positive for HER2 are being recruited.

Interactions between the different professional and patient groups involved in cancer therapy are facilitated by the National Cancer Forum¹³. This is an advisory body, established by the Minister for Health & Children in 1997 to advise on the implementation of the National Cancer Strategy. The Forum is multidisciplinary and representative of all levels of services and of consumers. The role of the Forum is to:

- act as a unifying link across all levels of cancer services for the purposes of planning and delivery;
- help ensure co-ordination of services;
- act as a focal point for best practice and the development and implementation of protocols;
- promote evaluation of the effectiveness and quality of cancer services and
- help co-ordinate research into cancer in conjunction with the Health Research Board.

This forum is one of the mechanisms employed to ensure coordination between the different levels of service involved in cancer diagnosis and treatment.

3.2.3 *Quality aspects*

The Irish External Quality Assessment Scheme¹⁴ (IEQAS) runs the quality assessment schemes for Irish hospital laboratories. However, the usefulness of such Quality Assessment schemes is dependent on the participation of a statistically significant number of laboratories. Because of the small throughput of HER2 analyses from Irish labs, IEQAS does not run a QA scheme for these tests. Irish labs providing these tests therefore participate in the UK QA scheme – NEQAS.

DakoCytomation (Ireland) claims that there are stringent protocols for performing the assays and continuous training and DakoCytomation provides support to kit users. The Association of Clinical Biochemists in Ireland (ACBI) is the major technical and professional body representing hospital laboratory staff in the country. This group is also active in organizing initiatives to ensure that their members are fully informed of these technologies and that training courses are available.

Guidelines recently introduced in the UK require that HER 2 testing should only be conducted in laboratories that have an annual caseload of at least 250 cases. Given that the FISH test is applied only in cases where HercepTest results are equivocal, if a laboratory with a low caseload produces a higher number of equivocal HercepTest

¹² www.icorg.ie/

¹³ www.nationalcancerforum.ie

¹⁴ <http://www.ieqas.ie>

results, expensive FISH tests are presumably applied more frequently than would be necessary in the case of a larger regional lab with a higher caseload.

3.2.4 Approval and reimbursement

In Ireland, health cover is provided within two categories: cover for medical cardholders and for all other categories.

Free Medical Cover:

Free Medical Cover is available to:

- Anyone under a specific income level, and their dependents
- Every person aged 70 or over
- Others with specific disease conditions, including some cancers

Approximately 1.15 million people (32% of the population) were provided with free medical cover as of December 2004.

Hospital cover:

At present everyone is entitled to hospital inpatient services in a public ward in all public hospitals. There is a €55 a night charge up to a maximum of €550 in any 12 consecutive months. These charges do not apply to medical cardholders. Higher rates apply for semi-private or private care.

Outpatient cover:

Attendance at the outpatients or Accident & Emergency (A&E) department of a public hospital, without referral by a General Practitioner (GP), may be charged at €55. There is no charge if referred by a GP. This charge does not apply to those with medical cards, or to those admitted to hospital as a result of attending the A&E department.

Drugs Payment Scheme:

Under the Drugs Payment Scheme (DPS) every citizen pays a maximum of €85 each month to cover the cost of prescribed drugs, medicines and appliances. The €85 limit applies to the total drug payments per household (i.e. spouses and dependant children). All costs above this amount are paid by the state.

Private Healthcare Cover

Private health insurance is used to pay for private care in hospitals (or as an outpatient in certain circumstances) or from various specialists in hospitals or in their practices. This is available through the state company Voluntary Health Insurance (VHI) and all employers provide the option of 'Group' insurance cover which has an additional cost benefit. All payments are also deductible from income tax.

In recent years other private health care insurance companies such as BUPA (Ireland) and others have also offered this service. They provide cover for day care/inpatient treatment and hospital outpatient treatment. Payments are fully tax deductible and subscribers can pay for whatever level of hospital care they choose.

Other forms of assistance, such as Disability allowance, also apply in particular circumstances.

Both Herceptin, and the tests required for Her2 screening, are covered by reimbursement procedures. Note however, that there is currently no cost associated with the Her2 testing as these kits provided free by arrangement with Roche.

3.2.5 Economic aspects

The low number of patients treated with Herceptin has obviated the need for any analysis of economic benefit to date. A report ¹⁵ on expenditure patterns and future funding of the five Dublin Academic Teaching Hospitals - (which includes most of the major cancer centres) indicates that the costs in 2002 of Herceptin 150mg treatments was €856,894. This would represent approx 900 vials of Herceptin. As the treatment for a single patient is in the region of 25 vials, this would suggest that only 36 patients received this treatment. An extrapolation of this figure to the national level would suggest that less than 60 patients receive this treatment per annum.

This estimation is supported by figures taken from the National Cancer Registry Ireland, which show that of the non-operative procedures conducted in the period 1994-1999, 10% of patients received therapeutic substances. This represents less than 40 patients per annum for that period. Therefore it is doubtful that any cost-benefit analysis would be undertaken for such a limited patient base.

With regard to the Her2 Test, the total market for tests is approximately 1700 per year, which is the annual number of new diagnoses. However, the test is provided to laboratories at no cost for the moment. The CB11 antibodies produced by Ventana, which are mentioned in the German report, do not seem to be in clinical use in Ireland, although they are used for research purposes. For instance, research at the Department of Surgery, NUIG has used Ventana DAB Map for studies on Membranous Her2/*neu* in Breast Carcinomas ¹⁶.

The total market for Her2 tests is in the region of 2,000 – 2,500 per year, which is the annual number of new diagnoses. The Irish market could be estimated at a minimum of 100,000 euros, but taking into account the research and clinical trial usage, it may be at least twice this amount. However, the test is provided to laboratories at no cost for the moment.

3.2.5 Social aspects: patients' attitudes

There are currently no societal issues related to the use of HER2 tests in Ireland. The Irish Cancer Society, which is a major independent source of information on cancer, carries information on this form of therapy without any reference to any significant

¹⁵ "Resourcing & Activity of Dublin Academic Teaching Hospitals – 1998 to 2002" Eastern Regional Health Authority

¹⁶ Research at NUI- Galway is reported in www.nuigalway.ie/surgery/research/

difference with other treatment types. Their current brochure ‘Understanding Breast Cancer’ contains a reference:

“In order to receive this treatment, your breast cancer cells must contain a certain gene called Her2. If you are positive for Her2, Herceptin may be used in your treatment. At this time, Herceptin is only used as an adjuvant treatment in the setting of a clinical trial.”

The staff of the Irish Cancer Society helpline were also surveyed on the issue of possible resistance by patients to the genetic nature of the HER2 test, or to other aspects of Herceptin use. In their experience, no patient had ever differentiated between the HER2 test and any of the other tests that are used in the process of cancer diagnosis or therapy monitoring. They also report, however, that Herceptin was not widely known among patients. This contrasts with the German experience, as reported in the Fraunhofer report.

None of the clinicians or laboratory staff interviewed had ever experienced any resistance by patients in relation to the genetic nature of the test, or of the therapy.

There is no single national policy with regard to human biological material use. However, all institutions have ethical committees which govern the ways in which materials are taken, stored and used. However, this may change in the future. The Irish Council for Bioethics¹⁷ was established in 2002 as an independent, autonomous body to consider the ethical issues raised by recent developments in science and medicine. The Council is funded by a grant from Ireland's National Policy and Advisory Board for Enterprise, Trade, Science, Technology and Innovation (Forfás).

A working group on Human Biological Material has been established by this group to examine ethical issues relating to the collection, use, retention and disposal of human biological material. The aim of the group will be to produce ethical recommendations for research in the area of human biological material.

Interviews

- 1 representative from Dept of Health & Children
- 1 representative from Dublin Molecular Medicine Centre
- 2 representatives from Irish Medicines Board
- Panel views from Irish Cancer Society patient helpline
- 1 representative from Irish Insurance Federation
- 3 representatives Hospital Clinical Laboratories involved in Her2 testing
- 1 Consultant Oncologist
- 1 Consultant Pathologist
- 2 Representatives of Dako and Roche (Ireland)

¹⁷ see: www.bioethics.ie

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3.3 The Netherlands

3.3.1 Introduction of HER-2 test and Herceptin in the Netherlands

In 1999, the company DakoCytomation was the first to introduce a HER2 test on the Dutch market, later followed by the company Ventana Medical Systems. In 2000 Herceptin from Roche was introduced on the Dutch market. It was not a joint approval of Herceptin of Roche and Herceptest™ of DakoCytomation as in the USA. However, Roche's does give a specific reference on the label of the drug to use a HER2 test (either IHC or Fish) but it does not specifically refer to a brand.

Before the introduction of both test and drugs, the Netherlands Cancer Institute (NKI) used a HER2 test on an experimental basis already in 1997. This high level cancer research institute is affiliated to a specialised cancer hospital (Antonie van Leeuwenhoek Ziekenhuis AVL), further referred to as NKI/AVL, and is located in Amsterdam. The NKI/AVL had developed an immunohistochemical (IHC) assay of HER2 status utilizing the 35B monoclonal antibody. This antibody detects an intracellular epitope of the HER2 protein. There is a high degree of correlation between a positive HER2 status using this

NKI/AVL-IHC test and HER2 gene amplification (van de Vijver, 2001). The NKI/AVL test was already in this period used for patients in the Anthonie van Leeuwenhoek hospital. However, the test results could not be used in the clinical practice until 2000 when Herceptin came on the market.

The NKI/AVL has an important role in the field of cancer research, diagnostics and therapy in the Netherlands. Together with the other nine comprehensive cancer centres (CCC's) in the Netherlands they provide the clinicians (oncologists) in the Netherlands with new expertise and methods in cancer research. It is one of their tasks to make sure that all patients in the Netherlands receive the same therapy and monitor the quality of it. Before the Herceptest™ of DakoCytomation was introduced on the Dutch market, NKI/AVL worked with the company to perform tests with the Herceptest™.

In other hospitals where interviews were conducted, the HER2-test was introduced later. In the Delfzicht Hospital, located in the northern part of the Netherlands, the test was first used in 2001. The interviewed clinician knew the test from literature and learned about it during a conference of the American Society for Clinical Oncology. In close collaboration with the pathologists from the regional Pathology Laboratory (P Lab) in Winschoten in North Netherlands and the clinicians from two other hospitals in the region that used the same P Lab, it was decided to introduce the test in practice. In this period the introduction of the test was made on the basis of decisions of individual clinicians. *'It is our duty to keep up-to-date'* according to one of the clinicians.

Later, in 2004, a more official decision to introduce the test was taken in consensus by the working groups 'Mamma-tumours North-Netherlands' of the Cancer Centre in North Netherlands (IKN). Similar procedures have been taken place for other regions and their cancer centres and related P Labs and oncologists.

In the Netherlands, each year about 11.000 women are diagnosed with a breast cancer; 20% of them have over-expression of the HER2 protein. It is the most common cancer found at women. Early detection helps to improve the prognosis for these women. In 2000, the Dutch Institute for Healthcare Improvement (CBO) formulated a guideline for the execution of population screening. This guideline comprises medical aspects, but also recommendations for the organization and communication within the care trajectory the women will pass through. In 2004 CBO and the National Breast Cancer Consultation Netherlands (NABON) published an interdisciplinary follow up of these 'screening and diagnostics' guidelines, but now for the treatment of breast cancer.

From January 2005 on, after the Dutch Society of Oncologists had accepted the guidelines of CBO/NABON, the test should be used for each breast cancer patient because it forms –together with other inputs - a basis for an informed decision on the therapy to be used. With this decision the tests are included in the hospital budget (see part 3 about reimbursement).

The industry has played an important role in the introduction of the test and drug. And as is the case for most companies in the field, they practice a very active marketing strategy.

DakoCytomation market its test by informing and training pathologists. Experts of the company assist the pathologists in conducting the test and help them to interpret the results and values. Test samples are sent to the pathologists so that they can practice the interpretation. Next to this, the company assists with “diagnostics over the phone; remote diagnostics over the Internet; on-site fault finding; preventive maintenance inspections; software and hardware upgrades; and providing warranty and service contracts.” (<http://www.dakocytomation.com>) For the FISH test DakoCytomation has developed an extensive e-learning training on the internet, and a newsletter is being sent in order to inform the professionals about new knowledge and prescriptions. Next to this, the interviewed company representative explained that they organize meetings (with support from Roche) to convince pathologists about the necessity to conduct the test in the right way. This is important because when a wrong decision has been made by a pathologist, the oncologist (clinician) will receive the wrong result and therefore is not able to give the right therapy.

Roche promotes the use of the HER2 test because, according to the interviewed company representative, they *‘prefer to sell the right medicine to the right person instead of selling the medicine to people who do not profit from it’*. In the Netherlands, Roche did not want to subsidize the test and/or the medicines, according to the interviewee from DakoCytomation, because *‘it did not work that well in the UK either’*. DakoCytomation argues that their cooperation with Roche on the Dutch market is important. Because of DakoCytomation’s relative small size they are able to contact each of the 60 pathological laboratories in the Netherlands, but visiting also the oncologists is not feasible for the company, according to the spokesperson of the company. And this is what Roche is doing. Both companies have organised a meeting for Dutch pathologists in order to inform them about the HerceptestTM and about the quality requirements related to the test.

One can conclude that clinicians/oncologists - especially those at the specialized cancer hospitals - together with the industry have played a leading role in the introduction and implementation of HER2 and Herceptin in the Netherlands. The influence of breast cancer patients on the introduction and diffusion process has been rather limited. Breast cancer patients already heard in an early stage after the drugs were introduced on the market in the US and later in 2000 in the Netherlands, about the use of HER2 test and Herceptin. However, test and drug were at that time only used in the research context of the experiments of the NKI and only for patients in the AVL hospital (for those that already had two chemo therapies). Nevertheless, both test and drug became known (Internet played an important role) and patients began to ask for it. They pushed the clinicians to do the test and, in case of HER2 over-expressions, use Herceptin. They also mobilised their patient organisation: the Breast Cancer Society.

3.3.2 *HER2 test and clinical practice*

In the hospitals in which we had interviews with clinicians, the test is now conducted as part of a standard procedure. It is part of a set of tests (including analysis of oestrogen and progesterone levels) depending on the characteristics of the tumour. According to Roche 25% to 30% of the breast cancer patients is tested HER2 positive. Market research of Roche showed that in 2003 one-third of the 110 hospitals used the HER2-test as a

standard. Another one-third did the test only on a special request of the oncologist, and the last one-third did not use the test at all. According to the company Herceptin is mostly prescribed in the western part of the Netherlands and only in a very few cases in the rest of the country. The influence of the NKI/AVL and the other Dutch specialised cancer hospital (in Rotterdam: the Daniel den Hoed oncology centre) are largely responsible for the integration of the test in the western part of the Netherlands.

According to the pathologist of the Winschoten lab, within 24 hours the results of a test for a breast tumour (for example armpit glands) can be given; the minimum time required for performing the IHC-test is twelve hours. This does not account for tumour tissues that have been treated with radioactive material. These take another three to four days before it is 'safe' to be analysed. The laboratory in Winschoten receives an average of three requests a week, which means an average of 150 tests a year. In the laboratory the practice is as following: One of the pathologists conducts the test while two others control the process. The final conclusion is made in consensus. The results are fed in the hospital's information system.

On the basis of the results of the HER2-test, the differentiation grade (1, 2, or 3) is calculated. When the differentiation grade calculated is 2+, a FISH test (genetic test) has to be made. These results, together with the information about the size of the tumour; the presence of glands in the chest; and metastasis, are the basis of the choice for a specific therapy, according to the interviewed clinicians and pathologists. However, even when the HER2 test is positive, Herceptin is not included in the therapy for all cases, at least not in all hospitals according to a clinician of the Delfzicht hospital. There are only two strategies there in which Herceptin is used: as adjuvant therapy (after a mamma amputation); or when metastasis has been found (in this case it will be used in combination with chemotherapy).

According to all interviewees, the introduction of the test did not have any heavy impact on clinical or laboratory practice. The introduction of the IHC tests did not ask for any specific extra implication measures; not much changed in the pathology practice. Only some logistics and organizational changes were necessary to fit the test in the existing structure. After the introduction of the test it was not necessary to adapt or change certain aspects of the clinical practice, neither in the NKI/AVL nor in Delfzicht Ziekenhuis.

Search for cheaper alternatives

The high price of the Herceptest™ and the Vyfis Fish tests are a serious barrier for the introduction and diffusion of the tests in the Netherlands. Roughly about 40% of the laboratories in the Netherlands that do the IHC test, use the Herceptest™, another 10% uses the Ventana test; the resulting 50% is what the DakoCytomation interviewee calls: "home brewed". The interviews have shown that new "home-brewed" tests are developed and used in order to reduce the costs. As mentioned already before, the Dutch Cancer Institute (NKI) has developed its own test. We learned through our interviews that the Winschoten based P-lab is involved in the testing and validating of another cheaper HER2 test. Together with the University of Maastricht (NL) and the university and university hospital of Bremen (Germany) they are developing a protocol for a new test;

an alternative to the FISH test of Vysis. The test is developed and will be marketed by Panpath. PanPath is a privately owned company, based in Amsterdam and in 2001 founded by scientists with a background in pathology and molecular biology.

In this project Roche is paying the bench fee for the three labs. Roche pays also the other costs of the German lab in Bremen, but not for the two involved Dutch labs. These are only two examples of “home brewed” tests; an overview of tests used in the SKKP quality procedure shows that there are much more.

DakoCytomation is not very happy with the ‘home-brewed’ tests, because *“the tests are not as good as ours and more important: it is hard to validate the results because every test is based on other parameters”*. On the other hand, the NKI/AVL claims that their test are as good as the DakoCytomation tests. The company now tries to negotiate about the prices of the tests, but it seems impossible to compete with a ‘home-brewed’ test that costs nearly 10% of the price of the Herceptest™. In other hospitals however, their standardized and approved test is still preferred, according to the interviewee of DakoCytomation.

3.3.3 *Quality aspects*

Especially because of the use of these “home brewed” tests in the Netherlands, quality is a point of discussion between the companies that bring the FDA approved test to the markets and other companies, hospitals and P labs that use or develop the “home brewed” tests.

According to the NKI/AVL clinician (who uses their own, very low-cost test) the more tests a laboratory conducts per year, the more laboratories are able to validate the test and to guarantee quality. According to Roche, the minimum is 150 tests a year in order to guarantee quality. The clinician in the NKI/AVL does not see any barriers in the introduction or use of their home brewed HER2 test: *“Because the hospital yearly conducts 300 tests, quality is guaranteed.”*

But also the use of the Herceptest™ (of DakoCytomation) has to be learned and validated. DakoCytomation provides a set of slides on their websites for control tests, and the three pathologists in the P lab in Winschoten used a protocol for the IHC test from the university lab in the region. In their learning process, they did a lot of tests on non lethal and lethal tumours and tests on material of which they already knew the results. Other inputs in this learning process were literature, information from the cancer centres and national working groups of the Dutch Society of Pathologists (NVP). They also used the FDA report that was made in the approval process for the Herceptest™ of DakoCytomation. The FDA report mentions also the types of problems that can be met when doing the tests, according to the pathologist of the P lab in Winschoten. The P lab also checked the outcomes of their test with the outcome of so-called reference centres, such as the university in the region that used another method. This internal learning process led the three pathologists finally to a point on which they agreed that they could conduct the test on the required quality level.

The PA lab in Winschoten is now in the process of introducing molecular biological methods in their lab, so they can do the FISH test themselves. Until recently this test was hardly used in the Winschoten laboratory. The few that had to be conducted (after 2+ indication based on IHC test) were sent to one of the few P laboratories in the Netherlands that have the expertise to do this molecular biological test. Winschoten will not use the DakoCytomation or Vyfis FISH tests, for cost saving reasons. As already mentioned above, they are involved in a project together with other partners, to develop a protocol for a much cheaper test developed by a small Dutch company.

Although the most important issue for the Breast Cancer Society, the patient organization, is the lack of information patients receive about diagnostic and therapeutic possibilities, the quality of the test is certainly not the least important issue for the Society: *‘It will remain very important to assess the quality of the tests. What do hospitals do when the budget is too small, and when they do not have the necessary knowledge and competences in-house?’*

The Breast Cancer Society has produced an information brochure about the interpretation of the pathologists report. It discusses questions like ‘what are you reading?’, ‘what does it mean’, and ‘what do certain terms and figures mean’? According to a spokesperson of the Society, this brochure is not everywhere perceived as a good initiative: *‘Although patients seem to be very happy with this information, clinicians often run it down because, according to them, it is not complete and useless’.*

Quality is the weapon DakoCytomation is using in the battle with the NKI/AVL and other P labs that use t “home brewed” tests. Because their test is FDA approved and IVD labelled¹⁸ (The European Directive 98/79/EC on In Vitro Diagnostic Medical Devices) they are in a strong position. DakoCytomation argues that an FDA sort of organisation is missing in the Netherlands and P labs even are not obliged to keep to GLP guidelines (Good Laboratory Practice). However, players like the NKI/AVL (which is a very highly qualified academic research institute and hospital that communicates publicly the importance of the validity and quality of the tests), are hard to combat for DakoCytomation.

3.3.4 Approval and reimbursement

Registration of Herceptin and HER2

Market access of new pharmaceutical products is covered by international regulations that have been implemented in the Dutch Medicines Act. The Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen – CBG) is the Dutch authority responsible for the evaluation and issuing of market authorizations for pharmaceutical products. Pharmaceutical products are evaluated on the basis of criteria that are defined in the Medicines Act; the criteria mainly address efficacy, safety and quality.

¹⁸ According to the directive, IVD manufacturers shall be obligated to systematically review the experience gained from the IVDs they have placed on the market; to implement corrective action if necessary; and to report incidents, near-incidents, and recalls to the proper competent authority. (<http://www.devicelink.com/ivdt/archive/03/09/001.html>)

The CBG carries out the evaluation on the basis of extensive dossiers submitted by the pharmaceutical companies, containing the required information from research studies. In general, two alternative routes exist for authorization of new pharmaceutical products: the centralized route at the European level by the European Agency for the Evaluation of Medical Products (EMA) and the decentralized route at the national level. For pharmaceuticals based on biotechnology only the centralized route at the EMA is possible. The Dutch Pharmacovigilance Foundation (LAREB) is responsible for the assessment and registration of adverse reactions of the pharmaceuticals, after market introduction (Enzing et al, 2005).

The registration of Herceptin as drug for the Dutch market did not cause any specific difficulties. Roche had to do a number of studies formally required for the registration.

Until 2002 the Herceptest™ and other test could be brought on the market without any formal registration. Since the implementation of the European Directive *in vitro* Diagnostics Medical Devices Kits of 1998 in the Netherlands in 2002, diagnostic kits are subject to legislation and have to have a code and to be labelled. The DakoCytomation interviewee complained that 50% of the tests used in the Netherlands, do not have these codes and labels, but at the moment no control mechanisms exist.

Unlike in the USA, the market approval in the Netherlands of the Herceptest™ of DakoCytomation and Roche's Herceptin was not combined. The spokesperson of the CBG mentions that in the market approval procedure for Herceptin in 2000 this has been discussed, but because there were also other HER2 tests already existing in the Netherlands, they did not want to exclude them. So the demands from the CBG were focussing on the required level of protein expression when Herceptin had to be used and not on the test through which these levels had to be measured.

Reimbursement

As the HER2 test and Herceptin are only used when the patient is in the hospitals, the costs of test and drugs are paid through the financial-administrative system of the hospitals budget. This is the virtual budget that each year agreed upon by national government, hospitals and health insurance companies. It is based on a set of parameters like numbers of beds, numbers of specialists et cetera but not on numbers and types of patients or quality of care. This budget sets the maximum for the costs for patient care that can be made by the hospital and that will be reimbursed through reimbursement. In addition Dutch hospitals have, since 2002, a special budget for expensive drugs; the so-called CTG guidelines (College Tarieven Gezondheidszorg – Committee Tariffs Health Care). This guideline says that maximal 75% of the costs of expensive drugs used by the hospitals are to be reimbursed.

However, hospitals have only a limited budget which implies that not all tests and drugs that are needed to give optimal patient care can be used. The average costs of treatment with Herceptin are 20.000 euro per patient. Per hospitals about 5 Her2 positive patients are treated with the drug, on an annual basis.

As a result, if a patient with breast cancer is the sixth or seventh breast cancer patient with a possible HER2 protein that year in the hospital, there is a very realistic chance that she will not be treated with Herceptin. Be tested and treated is very much neither depending on factors that are in the realm of patients, or that of doctors but depends on the hospital policy and the hospital population. Therefore patients – not only breast cancer patients but also patients that have to be treated with other expensive drugs - go ‘shopping’ in other hospitals (that have not yet exceeded their budget) and even go abroad - in order to get their treatment, according to the Breast Cancer Society. Bluntly speaking: it is a matter of co-incidence if a breast cancer patient gets the best treatment, despite the formulated guidelines of the CBO that stimulates all hospitals to use the HER2 test and use herceptin. A Dutch newspaper qualified this as ‘Roulette with pills: the lottery of Dutch drugs policy’ (NRC 26/27 March 2005). Some also qualified it as ‘Postal Code Care’. According to the Breast Cancer Society hospitals still often do not inform their patients as they should. ‘Ask, ask and ask again’ is what they preach to their members.

According to a spokesperson of the Ministry of Health, this situation could change with the introduction of the so-called Diagnosis Treatment Combinations (Diagnose Behandel Combinaties – DBCs) in the beginning of 2005. For each medical treatment in the hospital a DBC will be formulated. This implies that for the whole treatment a patient gets during her /his stay in the hospital only one account will be made, and not a separate bill for each part of the treatment. It is too early now to draw any conclusion on the impact of DBCs on the reimbursement of breast cancer diagnosis and treatments

Next to this, according to DakoCytomation, it would also improve if there was a reimbursement scheme specifically for pharmacogenetic tests. Furthermore, diagnosis and therapy should be regarded as a non-separable combination, argue Roche and the Breast Cancer Society as well.

3.3.5 Economic aspects

The size of the Dutch market for Herceptest™ tests is about 120.000 Euro; this is approximately 40% of the market. Ventana has about 10% of the IHC-test market. The remaining is “home brewed”. The share of the Dutch FISH test market for DAKO is approximately 60% (80.000 Euro). Abbott (Vysus) is their main competitor on the Dutch FISH test market. As we learned also here “home brewed” tests are being used. Roche only gave an indication of the Herceptin market in terms of numbers of patients. In the Netherlands there are 300-400 patients (with HER2 over-expression).

Using the test also affects the sales and use of other medicines like hormonal therapies because HER2 also provides information about the benefits and optimal combinations of other parts of cancer therapies. Therefore the sales of these therapies probably also have been, or will be, influenced, according to the interviewee of DakoCytomation.

3.3.6 Social aspects: patients’ attitudes

Patient organizations

At least 400 associations and organizations exist for patients with a specific disease or disorder. A number of them are united in umbrella organizations like the Dutch Genetic Alliance (VSOP) and the association for people suffering from chronic diseases and for handicapped people (Chronisch Zieken en Gehandicapten Raad Nederland, CG-Raad). Generally speaking, patient organizations represent patients' interests by improving awareness and understanding of diseases and disorders. The main activities of patient organizations are to spread information among their members and to communicate with government, public health authorities and welfare services in the political arena. Patient organizations try to influence the decision making processes, for example in the case of listing a new but more expensive drug under the public insurance schemes or the stimulation of specific health research areas. Patient organizations also communicate with pharmaceutical companies, especially with the more integrated (bio) pharmaceutical firms (Enzing et al, 2005).

The Dutch Breast Cancer Society provides demand-driven information services to breast cancer patients and people with a hereditary predisposition for it. It organises campaigns in order to raise patients' awareness of the possibilities to detecting cancer in an early stage and about therapies. It represents also the interests of the breast patients on several occasions and is a meeting place for breast cancer patients and their relatives.

The Society is very positive about the HER2 test: *'It is hardly possible to be against it, since patients only benefit from it'*. But, still patients receive too little information about the possibilities of the test, and the spokesperson of the Breast Cancer Society fears that some hospitals deliberately do not mention the existence of the test because of the costs of the drug. The Society mentions that market research showed that in 2004 85% of the clinicians waited until there is metastasis before requesting the test. According to the society, the Netherlands is far behind in the use of Herceptin when compared to Germany, Austria, France, Denmark, Belgium and the Scandinavian countries. The Society has developed therefore several information brochures, sometimes together with the pharmaceutical industry, to inform the patients.

The Society pleads for interdisciplinary and multidisciplinary mammacare teams which gives all breast cancer patients the possibility to be treated in a multidisciplinary way so that all necessary information from relevant specialists is available and also new scientific developments can be applied immediately. According to the spokesperson of the Breast Cancer Society there are only two or three hospitals that choose this approach in the Netherlands. The NKI/AVL is one of them.

Informed consent

For HER2 it is not common to ask informed consent in the assessed hospitals. The hospitals do ask for a standard statement of the patient in which she agrees with the hospital's policy to use human material for different purposes.

The clinicians interviewed mention that the patient does not receive technical information about all the ins-and-outs of the test, because it is seen as a standard procedure. Therefore, according to a clinician in the NKI/AVL, it is *"nonsense"* to ask informed

consent, simply because the test is part of a certain treatment of certain characteristics of tumours. *“If the patient disagrees, they are free to choose another hospital of their likings”*. As soon as it is shown that there is a genetic component in the breast cancer, the patient is forwarded to professional genetic counselling.

The other clinician argues that patients are informed about the fact that the HER2 test is about the existence of specific proteins in the cells. Existence of the protein means a bad prognosis and other treatments schemes. After the testing, the patients are informed about the results, in terms of positive or negative. If the result is negative, the test will not be further discussed.

Other social issues

In the report ‘Farmacogenetica’ (Pharmacogenetics) of the Dutch Health Council (Gezondheidsraad) published in 2000, another important social issue was mentioned: pharmacogenetic information possibly has consequences for the insurability and for employability in certain jobs. This is part of the more general discussion about privacy of genetic information. Besides this, certain genetic information can determine the use of certain expensive medicines. A last aspect is that certain information could be useful in the future for the prediction of risks on multifactor syndromes. In many countries there is poor regulation available concerning insurance and genetic information. The GR advised that it would be wise to formulate regulations and guidelines regarding genetic research, screening, diagnostics, et cetera, but according to a spokesperson of the Ministry of Health, there has been no serious follow-up of this advice since.

Interviews

2 representatives from the Ministry of Public Health, Welfare and Sports
1 representative from the College ter Beoordeling van Geneesmiddelen
2 representatives from the Stichting Kwaliteitstoetsing Klinische Pathologie
2 representative from industry
1 representative from a clinical-pathology laboratory
2 clinicians/oncologists
1 representative from the Dutch breast cancer patient society

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3.4 United Kingdom

3.4.1 *Introduction of HER-2 test and Herceptin*

Prior to the introduction of Herceptin to the UK market, very little HER2 testing was carried out in the NHS. About a year before Herceptin was to be launched, Roche carried out market research that showed that the UK had comparably low levels of HER2 testing. In Spain, France, Italy, and Germany about 40% of metastatic breast cancer patients were tested for HER2 overexpression, while in the UK only about 6% of patients were tested.¹⁹ Support for this claim can be found from talking to histopathologists one of whom suggested that the UK 'started with a very low base....There were very few centres that were routinely doing HER2 testing in breast cancer at that time....This contrasted with the States where I think it was close to 90 percent'.²⁰

The reasons that underpin this limited uptake of HER2 testing are varied, but they include the cost of the test and the subsequent effect on how clinicians view its clinical value. For Roche, this resistance was based on financial concerns, namely the UK's status as 'one of the worst countries in Europe for putting funding behind cancer drugs'.²¹ In addition there is a degree of scepticism about the value of such test within the UK oncological community. The histopathologist quoted above summarised it as: 'In this country there has been, and I think there persists, a thought that you don't do testing unless there is a real reason to do the testing'.²² In relation to HER2 testing, the result is that clinicians are doubtful over whether such a test is particularly useful in terms of the prognosis: 'It's largely irrelevant. In a way, in this context, it's more how the lymph nodes are positive, how aggressive is the tumour, what grade, what size is the tumour'.²³

This is clearly at odds with the position of the American Society of Clinical Oncology (ASCO) which has recommended that HER2 'overexpression should be evaluated on every primary breast cancer' (Bast et al 2001:1871) and the views of Roche who support the idea that HER2 positive tumours are resistant to some forms of chemotherapy and HER2 status is of value as a prognostic indicator.²⁴

The solution to this reluctance to test had two elements. Firstly, Roche aimed to overcome clinicians' cost-driven scepticism about the use of HER2 testing, and secondly

¹⁹ Roche Interview, 25/10/2002.

²⁰ Interview CR18 4/6/2003.

²¹ Roche Interview, 25/10/2002.

²² It is important to note that this scepticism is not just related to HER2 testing but should be seen as a broader community response. For example, similar resistance could be found to oestrogen receptor status testing, which identifies patients eligible to receive Tamoxifen.

²³ Interview CR2, 31/01/2002.

²⁴ Roche Interview, 25/10/2002

they decided to make Herceptin available to clinicians even though it had not been approved for use on the NHS. To get clinicians into the 'habit' of HER2 testing Roche's decided to fund all HER2 testing in UK, for a period of time running upto and past the introduction of Herceptin into the NHS: a solution that was described as unique to the UK and the Irish Republic. In essence Roche realised that: 'that the only way really we were going to... almost educate some of the doctors or persuade some of the doctors that this is a valid test, [was] perhaps by funding it'.²⁵ They did this by underwriting three HER2 'reference centres' based in hospitals in Nottingham, Glasgow and London.

From October 1999 to the end of March 2003, Roche allowed any clinician in the country to send samples for testing, free of charge. Although the company had planned to stop testing at the end of March 2002 the decision on the use of Herceptin on the NHS (see below) was delayed, and Roche continued funding the reference centres for another year. One aspect of this decision to carry on funding testing was the continued resistance from the testing culture: by March 2002, 'the testing situation had gone up to about 27% in the UK, metastatic breast cancer patients being HER2 tested, but the rest of Europe was ahead of 70-80%, so we were still quite far behind, so we felt that we should support it for a little longer'.²⁶ Since the 1st of April 2003, the references centres are no longer funded by Roche, but the company has maintained a degree of control over the UK HER2 testing, through working with one of the centres to provide HER2 testing, on a commercial basis, to smaller laboratories that might not be confident with their expertise.

Although Roche continued to fund testing at the reference centres for a year beyond Herceptin's introduction into clinical practice, the view of a number of clinicians is that the winding down of this funding could have been handled better. The 'warning that was available to labs in the country wasn't anywhere near as long as it might have been.' Since such labs have to plan well in advance 'to get new activity in place many months in advance of actually taking them on and really people weren't warned more than a couple of months [in advance]'.²⁷

As noted above, Roche set out to ensure not just that clinicians were used to HER2 testing, but also that they were prescribing Herceptin, even before the drug was approved for NHS use by NICE. Roche wanted to get the drug 'out there', to get clinicians using Herceptin, so that if and when NICE approved it, there would already be a degree of clinical experience. Roche's solution was to initiate an expanded access programme, an idea which is largely a result of AIDS activists in the late 1980s, who pressured companies into allowing them to take drugs before they had received FDA approval. This programme started in January 2000, making Herceptin available to 168 patients free of charge, as well as allowing the to be purchased by certain hospitals under special licence between December 1999 and September 2000.²⁸

²⁵ Roche Interview 25/10/2002

²⁶ Roche Interview 25/10/2002

²⁷ Interview CR18 04/06/2003

²⁸ Roche Interview 25/10/2002 / Interview CR4 1/03/02

Roche is still supplying Herceptin to at least one of our recent interviewees' patients who do not fit the strict NICE criteria.²⁹ Oncologists obviously appreciated this free of charge provision, although they accept that there are powerful commercial interests driving it: such a scheme was often referred to as a 'glorified marketing scheme'.

3.4.2 *HER2 test and clinical practice*

HER2 testing was introduced at different times for different hospitals. Some places in the UK, usually labs with a strong research interest developed HER2 testing in the late 1990s, while other hospitals, perhaps just down the road, didn't start testing until Herceptin became available.³⁰ Because of the Roche testing centres, there was no necessity to develop HER2 testing capacity as soon as Herceptin was licensed for use: when hospitals undertake their own testing, they use one or other of the approved tests (either the DAKO Herceptest or the trial antibody CB11).³¹ The introduction of Herceptin, prior to NICE approval, varied across the country; around half of all health authorities agreed to fund some Herceptin. Sometimes it took patients going to the press and campaigning to get this funding agreed.³²

The introduction of this testing faced two main barriers, both of which are still relevant. The first was financial. Oncologists describe variations in testing practice that seem underpinned by the (un)willingness of different healthcare organisations (hospital trusts and/or Health Authorities) to fund HER2 testing. While such funding was not an issue while Roche were underwriting the reference centres, since they withdrew funding, financial issues have become important factors in deciding whether HER2 testing takes place or not. The second problem involves getting access to tumour samples when a patient presents with metastatic breast cancer. These samples may be stored at another site resulting in testing delays of up to 1 month, or even 3 months in extreme circumstances.³³

Theoretically, oncologists agree that the best time to test patients is when they first present with breast cancer. Although HER2 status would not become relevant to treatment until the patient developed metastatic disease, such advanced testing would avoid problems with retrieving sample blocks at a later date when patients might require urgent treatment. *Actual* testing practice varies between centres. Some insist on testing all breast cancer patients on diagnosis, covering the costs of such testing using charitable 'soft' money.³⁴

In other places, testing might be offered to patients on diagnosis but a specific case has to be made ('if they're young and at high risk').³⁵ A recent press release from Roche suggests

²⁹ Interview senior oncologist 20/01/05

³⁰ Interview C2, 16/12/2002

³¹ Interview Oncologist 04/02/2005 / Interview 03/02/2005

³² Interview Oncologist 03/02/2005

³³ Interview Oncologist 03/02/2005

³⁴ Interview Oncologist 20/01/2005

³⁵ Interview Oncologist 04/02/2005

that ‘only 35% of cancer centres in the UK routinely test for HER2 status on breast cancer diagnosis’ (Roche 2005).

As already noted, the time taken to test is dependent on a number of factors, including the retrieval of tumour sample blocks from storage. Since tests are not run on an individual basis but are run in ‘batches’ there may be some delay once the sample has reached the lab. If the timing is right, then test results might be available in 24-48 hours. If a sample arrives just after a batch has been run, then it may take 7-10days.³⁶ Staff involved in this process include the clinician and staff in the histopathology lab (doctors and technicians).

3.4.3 *Quality aspects*

In the UK at least, Roche’s desire for improved quality assurance was helped, by of all things, the conservative testing culture which was the source of such low HER2 testing levels in the first place. Such low levels are an advantage since we in the UK: ‘haven’t got bad practice ingrained in the pathology community’ (CR18).

When Roche set up the its three reference centres to carry out free of charge HER2 testing, a panel of experts was appointed to oversee the testing practice in the three labs and develop quality control procedures. These procedures in turn fed into the NEQAS quality assurance scheme for HER2 which started in 2000.³⁷ This scheme has international links (particularly France) and is aiming to develop global standards.

There are around 100 laboratories in the UK carrying out IHC HER2 testing, all of which should carry out a minimum of 250 tests per year (For details of best practice see, Ellis et al 2005). To be accredited to the QA scheme, a lab submits to 4 assessments a year where slides from a laboratory are looked at by four assessors for staining and interpretation. If a laboratory fails twice it receives a warning. Another failure means that NEQAS can withdraw CPA accreditation. While this is not a *legal* requirement for a laboratory to carry out testing, most hospital trust Chief Executives would want to have their labs accredited, and most doctors would want their patients’ samples tested at a CPA accredited laboratory.

As has already been noted, a variety (perhaps as many as 30) of different antibodies can be used for IHC testing for HER2 over-expression, although in reality even where ‘home brew’ tests are used, only two or three antibodies are actually in use. Unlike the US, where the FDA has some control over ‘home brew’ testing, in the UK regulations are lax, and as a result it is the QA scheme that effectively ‘regulates’ the use of different antibodies in testing.

Data from the QA scheme suggest that the DAKO testing kit (used according to instructions) performs better than alternatives, and if a lab fails its assessments and is at risk of losing its accreditation one of the main points stressed by the QA scheme assessors is the accuracy of the ready-bought kits.

³⁶ Interview Oncologist 04/02/2005

³⁷ Part of the United Kingdom National External Quality Assessment Scheme for Immunocytochemistry (UKNEQAS-ICC) programme.

Although the accreditation procedure is relatively new, this form of ‘soft’ regulation holds out the promise of significant control over testing practice.

3.4.4 Approval, reimbursement and Economic aspects

At the same time as Roche was persuading UK oncologists to accept HER2 testing and Herceptin, the drug was undergoing review by NICE, the National Institute for Clinical Excellence. NICE’s role is to determine whether particular treatments are clinically and cost effective and thus whether they should be available on the NHS. Since it was set up in April 1999, NICE has come under a great deal of fire in both the medical and popular press, seen as a way of allowing politicians to surreptitiously ration healthcare (Smith 2000; Lipman 2001; Walker 2001). The NICE appraisal of Herceptin began in September 2000, lasted until March 2002, and was one of NICE’s more controversial decisions (Hedgecoe 2004). As usual during a NICE appraisal, a great deal of lobbying and publicity took place, with Roche, Breast cancer charities and clinicians all involved in efforts to persuade the Institute to produce a positive response.³⁸ Delays and problems to do with Herceptin were due to its nature as an anti-cancer drug which lacked Randomised Clinical Trial (RCT) data for monotherapy, since it is deemed unethical to run a control/placebo arm in the treatment of metastatic breast cancer, where, by definition, it is clear that current treatments are ineffective. NICE’s preference for RCT data meant that further reviews had to be carried out, delaying the final decision. The end result was limited approval for Herceptin, recommending that it be given to women whose tumours overexpress HER2 in combination with a chemotherapy (paclitaxel) in patients who have not received chemotherapy for their metastatic breast cancer or on its own, to women who have received at least two courses of chemotherapy, without effect (National Institute for Clinical Excellence 2002: 1).

It is important to note that NICE did not regard the Herceptin decision as special by virtue of the drug’s pharmacogenetic status: “The Institute makes its decision not on, is it pharmacogenetic?...[but]...on what the evidence is that’s available”.³⁹ Of course, it is quite possible that an organisation like NICE would be open to an approach which selected smaller numbers of patients for particular treatments. After all: “we’ve conducted 62 appraisals and 38 of them have been a selective recommendation, which means within but not all of the licensed indications. So 27 of the 41 drugs we’ve looked at are within a selective range of licensed indications. What that means is we’ve been able to target the drug at areas where they may be more clinically and cost effective. Arguably if this pharmacogenetic issue is true, then yes, you could say the targeting has been done for you. However, of course, if they are incredible expensive, then the overall analysis would still mean they might be clinically effective but not cost effective in that debate”.⁴⁰

³⁸ Roche interview 25/10/2002 / Charity Interview 19/06/2003 / Interview Charity 2 12/06/2003.

³⁹ Interview NICE representative, 07/07/03

⁴⁰ Interview NICE representative, 07/07/03

Since the then, all health authorities have been required to provide Herceptin to women who meet NICE's criteria.

A survey carried out by the UK Breast Cancer Coalition (an alliance of breast cancer charities) in September 2002 suggested that funding for Herceptin had come on-line, but that there was confusion over where exactly responsibility lay for monitoring provision (Breast Cancer Coalition 2003). More recently, concerns have been raised over the provision of HER2 testing by the charity Breast Cancer Care, whose Chief Executive noted "there is evidence that all eligible women are not having their HER2 status tested. NICE guidance on Herceptin was issued two years ago, and it is imperative that this guidance is fully implemented so that all eligible women with advanced breast cancer receive the best patient care and treatment possible. We believe it is essential that high-quality testing facilities for HER2 are in place throughout the UK" (Breast Cancer Care 2004). This is supported by one of our interviewees who suggested that by restricting provision of HER2 testing, health authorities were keeping Herceptin prescription costs down. Since they are obliged to give Herceptin to HER2 overexpressing women, by limiting the amount of testing carried out, they limit the number of eligible Herceptin recipients.⁴¹

For private health provision, the situation seems different. In terms of assessing the suitability of particular treatments, these organisations tend to accept a broadly defined 'clinical consensus' as supporting provision. In the case of Herceptin, the NICE approval served as a very public indicator of such consensus, and private health insurers seem happy to pay for this treatment. The problem they find is that because some clinicians are reluctant to send NHS patients for HER2 testing (perhaps because of economic worries), this reluctance carries on over into *private* patients, even though reimbursement would not be a problem. It is as if the HER2 'habit' that Roche tried so hard to instil in the UK Oncology community has been undermined by continuing funding concerns.

3.4.5 Social aspects: patients' attitudes

Patient organisations

In the UK, patients organisations pushed very hard for the introduction of Herceptin and continue to lobby for access to the drug in the NHS. In the case of Herceptin, there is no contra argument to the use of HER2 testing. HER2 overexpression is a requirement of both the pharmaceutical licence and NICE's approval and more than that, it is unlikely that clinicians would be willing to prescribe a potentially dangerous product without check to see whether a woman might benefit. Patients' groups do not seem to have a specific position on informed consent in HER2 testing (see below) other than a general preference for the need to respect patients' autonomy.

Informed consent

On the whole, patients in the UK are not told in advance that their tumour tissue is going to be tested for HER2 status.

⁴¹ Interview Oncologist 3/02/2005

When patients present in the clinic consent is gained for a biopsy to sample the tumour and patients may well be told that a number of tests will be run on the tumour tissue, but HER2 testing is rarely singled out for specific mention and the exact details of HER2 and Herceptin are rarely discussed with patients prior to the results becoming available. Therefore our interviewees could give no examples where a patient had refused a HER2 test, since they are rarely, if ever, informed of the test.

Oncologists do not ask for consent for HER2 testing for a number of reasons. First, HER2 testing is not the only test run on the tumour sample and time demands mean that it would be difficult to discuss the full range of tests run on a sample with each patient. Although Herceptin is viewed as a useful treatment, oncologists are unsure as to its status as pharmacogenetics, especially since the kind of genetic variation involved is not inherited and therefore does not raise many of the issues that 'normal' genetic testing does.⁴² In many ways HER2 and Herceptin has much in common with ER status testing for Tamoxifen prescribing decision, a practice that has been in use for 15 years. Finally, clinicians are wary about telling patients about Herceptin in advance of a positive result, since this may get their hopes up and result in disappointment in the case of a negative test (Hedgecoe 2004).

Some interviewees accepted that this is "a paternalistic approach... it probably won't last long, because they'll all ask for Herceptin".⁴³ In addition, a positive result to the HERA trial, suggested by recent research (Roche 2005) would also put pressure on the practice of 'protecting' patients from disappointing HER2 testing results: "It is going to be especially important if the HERA trial comes out to say that Herceptin is of value in the adjuvant setting. If that happens and we're saying why we're going to offer you Herceptin as part of this package of treatment following the operation, and patients will then go through knowing that bit more detail about their prognosis while knowing the HER2 result in that context".⁴⁴

Thus if clinicians' reluctance to provide full informed consent prior to HER2 testing is ethically problematic, it may well not remain a permanent aspect of clinical practice.

After a positive result, when the test and its treatment implications are explained to them, patients vary in their ability to get to grips with the mechanics of the test. Some have difficulty understanding what the test implies, but obviously this is far from all patients. In fact, in some cases patients present an actually ask for Herceptin; they have become aware of the drug and want to be tested for HER2 status.⁴⁵

Other social issues

The clearest issue mentioned by interviewees was the need for adequate funding of Herceptin and HER2 testing. Despite the requirements of a NICE approval, that all health

⁴² Interview oncologist 03/02/2005

⁴³ Interview C1 28/02/02

⁴⁴ Interview CR8 30/04/02

⁴⁵ Interview oncologist 03/02/2005

authorities provide Herceptin to patients with metastatic breast cancers which over-express HER2, provision is still patchy.

Methodology for UK Her-2 case study

The background to this case is a project exploring Herceptin as an example of pharmacogenetics, run from November 2000-October 2003. This involved interviews with 2 Clinicians and 20 Clinician Researchers. All of these people were medical oncologists except 3 histopathologists; those who self-described as clinician researchers tended to have research involvement in clinical trials rather than laboratory research. I also interviewed 1 laboratory researcher, 2 oncological pharmacists, 2 policy makers at a local healthcare level, one representative of NICE, one representative of Roche, and two people from breast cancer charities. These interviewees were selected from publications, clinical trials databases or snowball sampling.

A second round of interviews were carried out in Spring 2005 for the ESTO project. Names were selected from replies to the survey, covering three oncologists, three histopathologists and a re-interview with one of the oncological pharmacists previously interviewed. These interviewees were chosen to complement the first round of interviews and update information on clinical practice, economic issues and testing issues.

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4. Case studies: TPMT

4.1 Germany

4.1.1 Introduction of TPMT test in Germany

The TPMT polymorphism was described for the first time in 1980 in its phenotypic form, by the measurement of the patient's enzyme activity via red blood cell count (RBC, phenotypic characterisation). Around 15 years later, researchers discovered the first relevant genetic mutations (single nucleotide polymorphisms, SNPs) leading to this altered activity.

Yates et al. developed and validated polymerase chain reaction (PCR, genotypic characterisation) based methods for detection of TPMT mutations in the genomic DNA of humans. They established the genetic basis for TPMT polymorphisms and discovered that 3 groups of TPMT activities can be classified: homozygous wild-type, characterised by a high activity, heterozygous mutants, characterised by an intermediate activity and homozygous mutants with a complete deficiency.⁴⁶ They named the discovered alleles containing the G238C mutation TPMT*2, the G460A mutation TPMT*3B, and the A719G mutation TPMT*3C.⁴⁷ As logical consequence, in a next step, a variety of phenotype-genotype correlation studies have been conducted to show the specificity and sensitivity of the genetic mutations as predictor of individual drug response.

The most recent and largest study was conducted at the Dr. Margarete-Bosch-Institute, Stuttgart, Germany, by a research group around Professor Eichelbaum and was completed in 2004⁴⁸. The study included a population of 1,214 healthy blood donors. It was not only aiming at determining the accuracy of genotyping for the correct prediction of different TPMT phenotypes, it also included other external factors such as gender, age, nicotine, and caffeine intake. The work by Schaeffeler et al. demonstrated the high overall concordance between TPMT genotype and phenotype at a level of 98.4% with a sensitivity and specificity for genotyping at 90% and 99%, respectively. During this study new altered alleles were discovered that also play a (minor) role in the prediction of the phenotypic outcome. In February 2003, the biotech company EPIDAUROS as applicant together with the initial 'inventors' Matthias Schwab und Elke Schaeffeler applied for patent protection for the discovery of these new alleles. Altogether, 17 mutated alleles have been identified of which only three are widely common and therefore practically relevant (TPMT *3 was found to be the prevailing mutation in Caucasians)⁴⁹.

Another insight that was gained as part of the study conducted by Schaeffeler et al. was that there exists also a group of so-called ultra-metabolizers. The underlying reasons for

⁴⁶ Marra et al. (2002), p. 2507.

⁴⁷ Tavadia et al. (1999), p. 631.

⁴⁸ Schaeffeler et al. (2004)

⁴⁹ Schaeffeler et al. (2004)

this phenomenon are still unclear and whether a dosage adjustment for this group might make sense represents another research challenge.

The process of diffusion of this knowledge and the respective testing method is not easy as no financial interest of a great investor (compared to the Herceptin case) is involved. It is up to the clinical pharmacologists to educate oncologists and to diffuse the knowledge. A means for this are public conventions, congresses and articles in journals where the TPMT case has already often been a topic. A brief investigation in the archive of a common medical paper ("Deutsches Ärzteblatt") has revealed a total number of eight articles including the theme during a time span from 2000 until April 2005.

4.1.2 TPMT test and clinical practice

Despite the proof of effectiveness, the pharmacogenetic test is not yet obligatory in Germany. According to the FACHINFO FÜR ÄRZTE, only the regular measurement of erythrocyte status is compulsory. Whether this might change in the future along with the current FDA (efforts) effort "Guidance for Industry" is still an open issue.

Prospective determination of erythrocyte TPMT activity is currently advocated by experts as a routine safety measure before therapy to avoid drug toxicity. But this awareness is not yet common within the broad mass of physicians and it was stated that it will still take a while until the test will be widely established.

One interviewee that had conducted other studies in the field of leukaemia treatment had reported that it was rather university hospitals that were using the test and only in rare cases settled physicians depending on their motivation and capabilities, which corresponds to the impression of other respondents.

Most interviewed laboratories introduced the genotypic test about one or two years ago, but as described, it is rarely used. If measured at all, both methods –RBC and PCR- are generally (parallel) in use, whereas the measurement of the phenotype (red blood cell enzyme activity measurement) outweighs the genotype method enormously.

Yet, phenotyping has at least two serious limitations where only a genetic test makes sense. First of all, if a deficient or heterozygous patient has received transfusions with red blood cells from a homozygous wild-type individual, TPMT activity cannot be reliably determined by measuring enzyme activity within 30-60 days after the transfusion.

The second shortcoming of phenotyping is that thiopurine admission itself may alter TPMT activity in RBC with an increase of enzyme activity of approximately 20 % compared to baseline.⁵⁰ Because of this, the actual proceeding is to measure the phenotype if possible and to conduct genotyping only in the cases mentioned above.

One interviewed expert stated that the phenotypic test was much preferred as the genotypic test had not the same sensitivity referring to further studies. This has been disproved and is questionable according to current studies. This comment shows the later on discussed lack of confidence and knowledge of doctors. Supplementary, the method was said to be more expensive. The interviewee himself conducts about 5 PCR tests a year compared to around 850 RBC tests.

⁵⁰ Schaeffeler et al. (2004)

Yet, one has to bear in mind that only around 10 % of these tests are conducted in the field of ALL according to the interviewed person, whereas most are being ordered for the diagnose of intestinal diseases.

Another fact is, as one interviewee pointed out that the TPMT test is often only applied ex post to trace back the causation of the adverse reaction. This also corresponds to the recommended proceeding by a university.

There were several reasons mentioned to explain the fact that TPMT-testing is not very wide spread among physicians despite the fact that the benefits (at least in literature) outweigh the effort.

In literature, a discussion is often led on a presumed deficit in the physicians' knowledge regarding genetic issues.⁵¹ The apprehension that doctors are not enough skilled to conduct and interpret the test results adequately seems to be right. One interviewee stated that human genetics as subject during medical studies only became a compulsory prerequisite in 2000 in the course of the new approbation order. Taking into account the average age of a German doctor of 50.2 years⁵², many of them were not properly educated in this field. There is evidence that pharmacogenetics and pharmacogenomics will be more and more an integral part of the curriculum in German universities and that the next generation of young doctors might possess of a better genetic knowledge or will at least be sensitized for these issues. In general, the opinions to which extend this knowledge has to be achieved to apply PGx knowledge adequately diverges among the interviewed persons. The majority believes that very broad skills to explain the issue to the patient and to council the patient adequately are enough. Only in certain very vague cases, a human geneticist should be contacted. It was up to the laboratory to give an adequate instruction to the doctors. The problems that arise from this need will be thoroughly discussed later.

One interviewee already tried to push the knowledge by offering courses on the theme, but the rate of response was very low. Her explanation for that unwillingness to participate was that of an information overload - it was said to be hard to distinguish between relevant and useful information and not useful information regarding the whole bulk of news flooding the physician- and a lack of flexibility (a strong believe in the effectiveness of methods that are long in use and have proven to be good combined with an uncomfortability with adjustment to changes). There also prevails a lack of trust in the results of genetic tests as their result only represents one variable among many different ones leading to an altered reaction. Despite the proof of the rare influence of other external factors in the TPMT case this view dominates.

Another lab stated that a reason for the current hesitation is that scientists and companies hyped the theme very early when no application or proof of high correlation was on the market. Now it was seen as hard to revive this enthusiasm.

⁵¹ Kollek (2004), p. 109.

⁵² Ärztekammer (2005)

One more reason was said to be the rare frequency of occurrence of ADRs in many cases. The number of tragic or even lethal incidences can in time be prevented by regular monitoring of the patient.

One real drawback for not using pharmacogenetic information in advance is the fact that often no adequate data exists to guide the doctors what practical conclusions to draw upon the respective results. Even if such data does exist, there's often a lack of clear guidance or instruction on the adequate dosing proceeded. It is for example recommended to conduct a pharmacogenetic TPMT test and to reduce the individual dosage accordingly, yet, whether a dosage adjustment for homozygous patients to a level of 10 % of the standard dosage and for heterozygotes of 60-70 % is not fully evaluated.

One last issue is the fact that it is recommended even by strong advocates of pharmacogenetic testing to conduct the pharmacogenetic test supplementary to the regular thrombozyte monitoring (sometimes also referred to as Red Blood Cell Count; this does not represent a biochemical characterisation of the phenotypic status, i.e. the TPMT enzyme activity within the cells) and that the PGx test does not represent a substitute. According to expert opinion it was an undisputable fact that the "TPMT polymorphisms can only partially explain occurring panzytopenies and leucopenies, especially if they occur after more than four months after the commencement of the therapy." This leads to additional workload instead of less work for the physicians and additional costs.

An important prerequisite for the application of a new method is a clear reimbursement situation. As noticed in the interviews, respondents were not at all familiar with the current reimbursement procedures of the tests and a lot differing information was obtained by the interviewees. Yet, it was criticized that the reimbursed sum was not adequate compared to the real costs and efforts. This might partially depend on the new accounting settlement system recently introduced and further changes in the healthcare system.

Still, one could say that the general sensitivity for these correlations grows more and more but that this process will take its time.

Further attempts to develop and implement electronic prescribing and advisory systems in clinics can positively contribute to the development and diffusion of the knowledge. One interviewed lab, together with a university hospital currently attempt to merge two existing electronic databases to establish a combined database that contains very detailed information for doctors that prescribe a drug. The information exists of two parts. The first one is a warning system that is activated automatically when drug interactions might occur by prescribing a new drug. The other information is on the genetic know-ledge that is available for the drug in question. Therefore the doctor is warned immediately if adverse events might occur before prescribing the drug. If such a database would be more widespread/ common among doctors in the future, a lot would have been achieved in this field. By offering them the link to know more about the genetic pathways of a drug, this knowledge would automatically spread among the medical profession.

4.1.3 *Quality aspects*

With the wider dispersion of the tests, quality aspects gain in importance and a more complex interaction between the attending oncologist and a third party- which is either the clinical pharmacology or an external lab-, will be the consequence. The often claimed resulting time lag of this intermediation can be neglected according to an expert regarding the fact that no emergency medication is concerned but a lead-time to evaluate the alternative treatments in such severe diseases as leukaemia is always calculated.

In general, the proceeding is that the attending physician sends a blood probe to the affiliated (or external) lab instructing the laboratory physician what to do and awaits the result. In the case of an RBC (= phenotypic characterisation by measurement of the patient's enzyme activity) the turn-around-time was said to take up to five days. The test itself takes a minimum of 4 h and a maximum of 8 h. This includes washing of the sample, incubation and chromatography. In the case of PCR (= genotypic characterisation) the turn-around-time takes up to three days, depending on the overall workload. The test itself in the laboratory takes 2 h. Within the laboratory, no great adjustments had to be undertaken, as the basic tools and equipment were already available. If a hospital is equipped to carry out RBC itself the test results are available within half a day.

A much debated theme and a source for quality deficiency is the currently missing communication between the laboratory physician and the attending physician. Due to the multiple relations that exist either between gene mutations and exogenous or between endogenous factors, respectively, it is often the laboratory physician who would be better educated and who possess the latest knowledge. They should be part of the decision process on which tests to conduct and to choose among all possibilities given the right alleles that should be examined. Returning to the TPMT case, there's a wide range of known mutations, but only three are usually tested. The decision on what to test should be a common decision profiting from the combined knowledge of both disciplines.

Hence, laboratory physicians currently receive only in part of the cases an instruction by the physician what to test and no adequate data on the indication or supplementary clinical data. In return, they only forward the results that have been asked for. Within this predominantly common procedure, they can't give a better report to the physician who knows the patient and the circumstances. On the other hand laboratory staff often presumes a given stock of knowledge in genetic factors and forward a very short, fragmented report. Yet, the knowledge base is often not prevalent. Because of the complexity of these issues and the divided knowledge among the actors, their competencies should be bundled and a better communication in both directions (top-down from the attending physician to the laboratory physician and bottom-up from the laboratory physician to the treating physician) should be warranted. The system could realise synergies and the patient would certainly receive a better treatment.

Some hospitals have already introduced a three-step approach with feedback loops between laboratory physician and attending physician⁵³. One laboratory physician saw

⁵³ IGLD Symposium, Panel discussion, 04/03/2005.

his job as a "consiliary service" to "council the colleagues at the front-line". This should be further advocated to ensure an adequate use of pharmacogenetic testing.

In Germany, tests are either conducted in a clinical pharmacology or in an external laboratory. Within the interviews it was discovered that the results gained in both settings vary in respect to quality assurance and the proceeded report. Whereas most commercial laboratories tend to follow the voluntary accreditation system, most internal (hospital) labs are not accredited as there does not exist a compulsory accreditation system for labs. Table 13 compares the German process relevant for accreditation and certification (Schüttpelz 2003).

Table 13 Characteristics of accreditation and certification

<i>accreditation</i>	<i>certification</i>
according to EN 45020	according to EN 45020
accreditation is defined as : "procedure in which an authorised institution gives the formal credit, that a centre or person is competent to fulfil a specific job"	certification is defined as: "procedure in which a third party confirms in writing, that a product or a process or a service is consistent to defined requirements"
that means: accreditation = approval of competence	that means: certification = approval of conformity
It is demonstrated that a e.g. laboratory	It is demonstrated that an organisation
<ul style="list-style-type: none"> • follows a quality management system • is technically competent to fulfil a minimum of technical requirements and is capable to gain well-founded results 	<ul style="list-style-type: none"> • follows a quality management system according to the requirements of DIN EN ISO 9000:2000.

The European Commission recommended all member states to establish a central accreditation system according to the examples in France and the UK. In Germany a national accreditation system was initiated in 1989. The German Council for Accreditation (Deutscher Akkreditierungsrat (DAR)), founded 4 March 1991, coordinates national and federal accreditation activities and a balance of interests between the compulsory sector (e.g. environmental requirements) and the private sector that is not regulated by law (e.g. test laboratories with new products).

According to interviewees medicinal laboratories follow accreditation systems for marketing reasons though smaller laboratories hesitate due to the high costs and bureaucratic and time consuming procedure.

Commercial providers of diagnostic testing services have to assess the quality of their offered services regularly. Paragraph 4a of Medizinproduktebetriebsgesetz (MPBetreibV 2002) states that results of measurements have to be guaranteed via regular check-ups

(internal quality assurance) and via participation at comparison studies per quarter (interlaboratory tests/ ring studies- external quality assessment).

Parallel to this attempt to regulate the quality of medical devices and linked services, the German Federal Medical Association has released a guideline on the "quality assurance of quantitative laboratory analysis" that has come into being with the year 2003. Attached to this regulation, there's a list of included norms and allowed deviations from given benchmark values.

In the case of contractual services, this certification also serves as prerequisite for the reimbursement decision for quantitative laboratory services. Therefore a financial indirect coercion to participate exists as well. Within the standard charging list (EBM), it is noted that these services are only billable, if quality requests by the German Medical Association are being fulfilled.⁵⁴

4.1.4 Approval and reimbursement

PGx applications consist of a pharmaceutical/diagnostic test combination. Prerequisite to grant save applications in this new field is an effective approval process. So far, no pharmacogenetic specific process for approval has been designed in Germany. At present two different bodies of authority are responsible both for the approval of pharmaceuticals and the validation of medical devices.

Apart from some specific exceptions that belong to the scope of responsibility of the PEI, the approval process of pharmaceuticals and the validation of medical devices are incumbent on the BfArM. The PEI is responsible for the approval of immune-biological pharmaceuticals, such as serums, vaccines, blood products, test allergens, test sera und test antigens as well as the validation of in vitro diagnostics. With the conversion of the EU in-vitro diagnostic directive into German law in the course of the German "Medizinproduktegesetz" (law on medical devices), a new testing laboratory has been established within the PEI, the so-called PEI-IVD. Since the end of the year 2003, this especially dedicated laboratory cooperates with other 'notified bodies' in the field of in-vitro diagnostics.

As the respective products (Imurek, PuriNethol,...) are all long established on the market and gained approval before the genetic knowledge came apparent, they've not been touched by this problem. Whether already approved products will be re-examined in the future is an open question.

The German reimbursement situation is not only determined by the separation of the market into public and private insurance schemes but also depending on different bodies of rules and regulation in different in- and out-patient settings.

German physicians- contractually physicians (settled/out-patient sector) and clinical physicians (in-patient care)- settle their services according to four different bodies of rules and regulation:

⁵⁴ Kassenaerztlichen Vereinigung Niedersachsen (2003)

- "Einheitlicher Bewertungsmaßstab" (EBM) for contractually services
- "Gebührenordnung für Ärzte" (GOÄ)
- "UV-GOÄ", agreement between physicians and casually insurance carriers
- Diagnose Related Groups (DRGs)

The EBM applies for performed services in the out-patient/settled sector and for general practitioners with hospital affiliation. All patients belonging to a statutory health insurance scheme are subsumed here.

Within the GOÄ, performed out-patient as well as in-patient services for privately insured and other cost carriers such as civil servants are being deducted.

The UV-GOÄ is not relevant in the field of PGx. It accounts for performed in- and out-patient services that are deducted via statutory casualty insurances such as Accident Prevention & Insurance Associations.

Supplementary, Germany ran through a fundamental reform concerning hospital services. The former system of day rates has now been displaced by a system of so-called Diagnose Related Groups (DRGs). These case-based lump sums were already introduced on a voluntary basis from January 1 2003 on and have become mandatory with effect from January 1, 2004.

Additionally to these profound changes, a new EBM, called "EBM 2000 Plus" has been launched at the beginning of this year. These changes led to a quite big confusion among concerned physicians that was reflected within the interviews.

Within the first two studies of rules (EBM, GOÄ), products and tests are being reimbursed separately. PCR and RBC specifically, are being reimbursed in both cases. Yet, physicians claimed that, especially in the case of RBC which is far more wide spread, the refunded sum did not cover the actual costs, which might represent a hurdle for further diffusion of the application.

Concerning the DRG solution, diagnosis as a whole are the considered unit and all needed materials and services are subsumed under this sum (DRG R61 in the case of acute lymphatic leukaemia.) There only exist different gradings that account for the occurrence of possible complications. Also pharmacogenetic tests would belong to this overall budget for the diagnosis.

Regarding further future PGx applications, it is always up to the Federal Joint Committee (G-BA) ("Gemeinsamer Bundesausschuß"), the German common board of physicians and insurance companies to decide upon the reimbursement situation. Talking to representatives of private insurance companies, they claimed to usually follow the decisions reached by the G-BA.

As there are also misunderstandings in the field of "will the treatment done be reimbursed" further communication between the attending physician and the controlling department should be advocated.

4.1.5 Economic aspects

According to the Robert-Koch-Institute, there were 5,151 new cases of leukaemia in Germany in the year 2000. Of these, acute lymphatic leukaemia is said to have the highest proportion of 27.4 %. Therefore, the number of new incidences must amount to around 1,411 cases per year. Unfortunately, due to the fact that there exists no common registration of new cancer incidents in Germany, this is the latest reliable figure available. Within the treatment of ALL, the immunosuppressive azathioprine is of high value. However, the incidence rate of severe side effects linked to the application of azathioprine and its metabolic product 6-mercaptopurine (6-MP) is quite high as can be viewed in table 14.

Table 14 Azathioprine-linked side effects and frequency of occurrence

<i>side effect</i>	<i>incidence rate</i>
Myelosuppression	1-2 %
panzytopeny	2-11 %
leukozytopeny	very rare
thrombozytopeny	very rare
anemiy	
hepatotoxicity/ cholestase	2-5 %
pancreatitis	2-4 %
sickness, vomiting, lack of appetite, diarrhoe	2-5 %
infections	7 %
other side effects	~ 2 %
fever, skin rashes	up to 15 %
arthralgy, gyalgy, general feeling of sickness	
single reported cases pneumonitis	
acute interstitielle nephritis acute vein	
occlusive arterial disease of the liver (VOD)	
noduläre regenerative hyperplasy of the liver	

Source: personal communication with M. Schwab

Newer studies prove that great parts of these side effects can be attributed to different genetic make-ups.

The use of PGx to individualize drug therapy is said to offer the potential to improve drug effectiveness, reduce adverse side effects, and provide cost-effective pharmaceutical care. This claimed cost-effectiveness has yet to be proven.

In practice, cost-effectiveness analysis as a quantitative framework to evaluate health care technologies is not a routine measure to decide upon the approval and reimbursement of a new entity. The actual evaluation is carried out on existing data and judgement.

This situation is reflected when searching for cost-effectiveness analysis in the field of Herceptin and TPMT measurement. Regarding the two case studies, there are only very

few studies available and none of these was conducted in Germany. Nevertheless, they can give a clue for the actual cost-benefit situation.

Three studies were found that attempted to quantify the net cost-benefit effects of pharmacogenetic tests in the case of TPMT testing that will be explained more thoroughly below (table 15).

Table 15 Survey of studies found

<i>authors</i>	<i>year</i>	<i>origin</i>	<i>type pf study</i>	<i>result</i>
Tavadia et al.	1999	Canada	cost-effectiveness	favours PGx test
Marra et al.	2002	Canada	cost- effectiveness	favours PGx test
Winter et al.	2004	Scotland	cost-benefit analysis	favours PGx test

Source: own demonstration

The mentioned studies also include the fact that genotyping is only a supplementary means to avoid side effects, but no substitute to regular thrombozyte measurement. Even strong advocates of pharmacogenetic testing methods agree in this point as not all adverse reactions can be explained by genetic predispositions.

Different actors of the health sector, such as insurance companies, said that it was much too early to quantitatively evaluate economic consequences. In the case of TPMT, the advocates of pharmacogenetic TPMT testing are unanimously convinced that benefits outweigh the costs.

Nonetheless, reliable German data is still missing. There exists one study comparing the costs of different treatments in the field of leukaemia stating that there exist large differences in costs regarding different case studies.⁵⁵ This observation can in great parts be attributed to the treatment of side effects according to the author.

The concerned pharmaceuticals are all long established products on the market (Imurek, Azathioprin). The only former restriction to the use of the drug was a warning to regularly monitor the patient's thrombozyte status and to quit treatment if a critical value has been reached.

The introduction of a diagnostic test as a means to sort out certain patients is principally contrary to a firm's financial interest. It was not possible to get to know whether any financial effects have been noticed with the introduction of the test on the side of the concerned pharmaceutical companies, but one might assume that the use of the test is still too uncommon.

Regarding former cost-effectiveness studies, one could also assume that given the actual distribution of different genotypes and the currently recommended dosage adjustment, the pharmaceutical company could even gain from adjusting the dosage. Another

⁵⁵ Teubner et al (2004)

possibility that is not yet clinically proven is the possibility of adjusting the dosage for so-called ultra-metabolizers accordingly. This possible incentive was briefly reflected with experts, but seen as too difficult in practice, e.g. due to the current application method via pills that would somehow have to be adjusted in dosage which would lead to additional costs in production and packaging. There's currently no more adequate incentive for the pharmaceutical firm to experiment in this respect.

Another issue that is worth mentioning are current efforts by diagnostic companies to develop more and more chips to facilitate the transaction of testing. This might be helpful in certain cases, where a large number of polymorphisms is simultaneously concerned, but not in the case of TPMT. In the words of one interviewee "It is easier to run three small PCRs" than to implement and finance a special diagnostic test. Overall, these tests were seen as much too expensive to be successful on the marketplace.

4.1.6 Societal aspects: patients' attitudes

"The affected individual is willing to try everything
that provides the slightest chance of help."

This was the most common statement among interviewed persons. As both considered indications are life-threatening, this knowledge represses all other feelings of doubt.

Regarding the potential benefits that can be derived from pharmacogenetic applications for patients, there was a clear consensus among the questioned parties. The safety of medicines in terms of an avoidance of adverse reactions was predominantly formulated. Also reported was a potential higher rate of patient compliance due to more "individualized" therapy options. A common counter-argument concerning a potential rise in compliance was that patients discontinue taking medicines because of the possible occurrence of side effects that can't be reduced by better targeting the medication (such as loss of hair, virility problems, etc.).

Various ethical or societal problems that might occur in the course of introducing pharmacogenetic methods were reported. Among them were data protection fears regarding misuse of this data on the side of insurance companies and employers, as well as the storing of probes within clinical trials and anonymisation of the data raised. Another point of discussion was the eventual elevation of supplementary information and how to deal with it in the case of occurrence. Concerning these issues, very controversial opinions were recorded.

Whereas physicians and laboratory staff as well as representatives of companies play down the issue and compare the data raised to "blood group determination" and "colour-blindness", patient groups and authorities are more cautious.

Regarding the derivation of supplementary information in respect to a predisposition to other diseases, opinions also diverge. Two reasons were stated that speak against a potential problem:

Firstly, only one correlation was found up to now (arylamine N-acetyltransferase 1 (NAT1) and a possible predisposition to urinary bladder cancer) despite further progression in research and secondly, these correlations are characterized by a multi factoriality – even in the case of NAT1- that the real probability of developing the disease in question is really rare. Still, the counter-argument is that the field is very immature and further research might reveal other critical correlations. A difficult question raised was how to react, if a correlation is detected ex-post- tell the respective patient or not? These issues have to be cleared now and current regulatory efforts are on the way.

TPMT was seen as the best example in the field of PGx, as a genetic polymorphism is screened for that would disturb nobody under normal circumstances. "A homo- or heterozygous patient can become 150 years old without any disturbances because of that." Or in the words of another physician: "On a disease predisposition, e.g. Alzheimer, one has to test specifically, such an information does not simply occur."

Supplementary, in the case of TPMT, a very small variety of products is influenced very strong by these mutations, whereas in other cases, a wide range of medicines is influenced very slightly, as in the case of CYP2D6. Therefore, TPMT is really worth testing without having to fear any impact in other areas.

The biggest concern on the part of the patients is a lack of time allocated by physicians to council the patient. They feared that this problem grows even more acute in the view of the scope of the decision to take. Even now, more and more patients start seeking for information on their own as they don't feel adequately informed by the doctors. Whether –at least in certain cases- a human geneticist was to be contacted was not agreed upon. Considering the poor state of knowledge among physicians themselves regarding these correlations, it is no wonder that patients are not at all familiar with existing possibilities and risks. The theme represents a topic at medical congresses and in professional journals that don't reach the broad public.

As stated above, no company's commercial interest is involved in the issue. Therefore, no action is undertaken to directly educate the patient. Because of existing information asymmetries as common problem in the evaluation of a physician's performance, the patients are dependent on the doctor's competence and willingness to anticipate these new currents.

Interviews

- 4 Research Laboratories (Dr. Margarete Fischer-Bosch-Institute for clinical pharmacology, Stuttgart; Institute for Pharmacology, Kiel, Insitute for Clinical Chemistry and Laboratory Medicine, University Regensburg, Department for Clinical Chemistry, University Göttingen)
- 3 Clinical Laboratories (Laboratory for Medical Genetics, München; Centre for Laboratory Medicine, Microbiology and Human Genetics, Mönchengladbach, Department for Medical Genetics and Genetic Advice, University Würzburg)
- 1 specialist doctor for human genetics (Würzburg)
- 3 Officials of Sickness Funds (Münchner Rück; Hamburg Münchner Krankenkasse, DKV Köln)

- 3 Company representatives (Wyeth Pharma, GlaxomithKline, Verband der forschenden Arzneimittelhersteller (=German Association of Research Based Pharmaceutical Companies)
- 2 Officials from the Medicines and Healthcare Products Regulatory Agency (PEI, BfArM)
- 2 Representatives of Patient Organisations (Cancer Association Baden-Wuerttemberg, Cancer Association of Berlin)
- 1 Official of the German Parliament
- 1 Official of an ethic commission
- 1 Official of the Central Authority of the Laender for Health Protection Regarding Medicinal Products and Medical Devices

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4.2 Ireland

4.2.1 Historical overview

Background information: ALL

In the Republic of Ireland, an average of 350 new cases of leukaemia were diagnosed annually between 1994 and 2002 (Fig. 1). Approximately 111 of these cases are in children ⁵⁶. Of these, an average of 206 were in males and 144 in females in each year.

A recent study of the combined statistics for Republic of Ireland and Northern Ireland showed the following key facts ⁵⁷ about Leukaemia:

- Average of 368 new cases per year, 1994-2000: 153 per year in females, 215 in males.
- Average of 247 deaths per year 1994-2000: 111 in females, 136 in males.
- Age-standardised incidence and mortality rates about 70% higher in males than females.

The majority of cases in the 1994 – 2000 period were lymphoid leukemia's (52% of all leukaemias). Of these, acute lymphoblastic leukemia was the most frequent diagnosis in children (67% of all children with leukaemia), and chronic lymphocytic leukaemia (CLL) was the most frequent diagnosis in older patients (37%). The remaining cases were mainly myeloid leukaemias (35% of all cases, and 14% of childhood cases).

These statistics, and confirmation from the leading Irish clinic involved in acute lymphoblastic leukaemia (ALL) treatment, show that the annual incidence of ALL in Ireland is approximately 30-32.

Table 16 Annual Episodes of New cases of Leukaemia ⁵⁸

	1994	1995	1996	1997	1998	1999	2000 *	2001*	2002 *
All Cancers	9679	9429	10008	10231	10215	10342	10610	10836	11077
Leukaemia									
Female	157	115	141	152	162	131	145	147	148
Male	185	208	192	204	205	207	213	218	223
Total	342	323	333	356	367	338	358	365	371

* Estimate

Mortality 1994-96

Annual averages of 123 deaths among females and 162 deaths among males were attributed to leukaemia: about 3 deaths for every 5 incident cases. Mortality rates (EASRs) were significantly higher in males than females, by about 71% (95% confidence

⁵⁶ Average annual incidence of childhood cancers in 1998 – 2000 was 111

⁵⁷ Source: Ireland-Northern Ireland-National Cancer Institute Cancer Consortium: www.allirelandnci.org/

⁵⁸ Source: National Cancer Registry – Republic of Ireland only.

limits 49-98%). On average, Irish females were estimated to have a 1-in-340 chance, males a 1-in-205 chance, of dying from leukaemia by age 74. The 5-year survival rates determined in the All-Ireland study are in table 17.

Table 17 Five-year relative survival for patients diagnosed in 1995-1997 or 1998-2000

Cancer type	Females		Males	
	1995-1997	1998-2000	1995-1997	1998-2000
Leukaemia	48.8	45.3	39.0	42.8
All invasive cancers	47.7	50.4	38.4	43.9

In contrast to most other cancers, substantial rates of leukaemia were recorded in the youngest age-classes (0-4 and to a lesser extent 5-9 years) in the joint ROI/N.Ireland study ⁵⁹. This largely reflects rates of acute lymphoblastic leukaemia, which peaked in age-class 0-4 (5.2 cases per 100 000 females, 6.8 per 100 000 males). Rates were low, and relatively constant, from about age 10 to 40, but increased rapidly thereafter (especially from about age 60 onwards).

There was no consistent difference between male and female rates up to about age 60, but rates in older males were much higher, and showed a more sustained increase with age, than in females. Median age at diagnosis was 67 years for females and 66 years for males.

Background information: TPMT Testing

Irish hospitals have historically each had their own in-house analytical laboratories and there is currently no move to centralize such testing. Cancer therapy is, however, centralized within certain hospitals and therefore specialized testing such as TPMT will only be of relevance to laboratories within these specific hospitals.

TPMT deficiency can be assessed by two means:

- An enzymatic test using blood cells from the patient. This is the usual test conducted. It is a simple test in terms of reagents used, but can be laborious and lengthy. This probably means that laboratories group the test and therefore test results may be delayed. Our estimate of cost, based on interviews and analysis of reagent needs, is approximately €50 per test.
- A gene-profiling test which screens for mutant alleles associated with TPMT deficiency. Many labs have developed such tests and there are also commercial assays in development. One such assay is the PRO-predict® TPMT Genetics test by Prometheus laboratories⁶⁰. No usage of this or other commercial genetic assay was found in Ireland.

⁵⁹ Source: Ireland-Northern Irl-National Cancer Institute Cancer Consortium: www.allirelandnci.org/

⁶⁰ Product information is at: www.prometheuslabs.com/212a.asp?nav=products

The incidence of TPMT deficiency is in the range of 5-10% of patients. A clinical study conducted by Dr Fergal Moloney ⁶¹ of Beaumont Hospital, Dublin screened 500 (mainly adult) dialysis patients who were receiving azathioprine. In this study 7% of the patients were TPMT heterozygotes.

Dr Owen Smith of the Our Lady's Hospital for Sick Children, Dublin reported that between 5 and 10% of children presenting with Leukaemia tested positive for TPMT deficiency.

The National Centre for Medical Genetics⁶² in Our Lady's Hospital for Sick Children is conducting genetic testing of children with ALL, but mainly for research purposes. The main screening of patients is that conducted by the Sheffield laboratory (see 1.2). Our estimate of the cost of genetic testing, is approximately €250 per test.

The range of purposes for which TPMT testing is conducted complicates assessment of the extent of TPMT testing for ALL in Ireland. Although a small number of hospital laboratories conduct their own TPMT testing, many samples from Irish labs are also sent to Guy's Hospital in the UK. An analysis by the Guy's Hospital laboratory of the range of requests which they have received in the past would seem to also reflect the range of uses from Irish labs. In all, the study (Holme *et al* – see reference 3) showed that TPMT testing was requested by 13 different medical specialties, of which Dermatology and Gastroenterology were the most frequent users, together accounting for 86% of requests. Requests from Oncology clinicians accounted for only 0.6%.

An interview with a Clinical scientist in a Limerick Hospital confirms this pattern of TPMT testing. Although they receive only 30 requests for TPMT tests per annum, the requests are mostly from dermatologists (80%), followed by gastroenterologists. Because of the low level of requests, samples are forwarded to Guys Hospital in the UK for analysis. The Limerick laboratory noted that there is a growing demand for the tests from medical consultants.

A consultant biochemist in a Cork hospital receives requests for approximately 50 tests per annum, and these are mainly from Gastroenterologists. This laboratory is conducting its own tests. The tests used the standard enzymatic test, and they are also developing also an additional test based on Real time PCR in association with a local college research group. The protocol is developed by combination of self and commercial information. This interviewee also noted that TPMT is fast being considered as a must, both to inform treatment doses and also to avoid adverse drug reactions within genetically vulnerable individuals.

4.2.2 TPMT testing and Clinical practice

The major centre for treatment of children with Leukaemia is Our Lady's Hospital for Sick Children⁶³ in Dublin. All Irish children presenting with Leukaemia are routinely

⁶¹ Interview with Dr Moloney.

⁶² www.genetics.ie/research/leukaemogenesis-lateral-sclerosis/

⁶³ www.olhsc.ie/Departments/OncologyHaematology/

tested prior to treatment. This is mainly for clinical reasons, as it is useful both to identify TPMT-deficient patients, and also to individualise the dosage. It was also noted by clinicians that medicine is now practiced in a highly litigious environment. Failure to test could result in malpractice in the event of the occurrence of side effects, and this is also a motivation.

Our Lady's hospital treats approximately 30 children newly diagnosed with ALL per year. In addition, there are approximately 5 to 7 relapse children per year. Patients usually undergo an induction phase of specific diagnosis, and initial therapy determination during which an appropriate dosage is determined. This is followed by a treatment phase with 6-Mercaptopurine, which generally lasts 2 years for boys and 1.5 years for girls.

All of the Irish ALL patients are also enrolled in the UKALL clinical trials, which are coordinated by Dr. L. Lennard in Sheffield. This is voluntary, but has been taken up by virtually all patient families to date. This trial is described fully in the UK WP2 Report.

A full genotyping is also conducted as part of the protocol for this trial. The proportion of children who experience problems with TPMT sensitivity, which are severe enough to require hospitalisation, is 5–10%⁶⁴.

Clinicians have noted that acute lymphoblastic leukaemia can be difficult to diagnose (Ref 2). The diagnosis is often obscure when the patient is first seen¹.

4.2.3 Quality aspects

There is no special quality assurance scheme for TPMT tests conducted in Irish laboratories, but the standard of testing is assured by the normal quality systems operated by laboratories.

4.2.4 Approval and reimbursement

In Ireland, health cover is provided within two categories: cover for medical card holders and for all other categories. All treatments using TPMT-relevant diagnostics and therapies are fully re-imbursable in both systems of medical cover.

Free Medical Cover is available to:

- Anyone under a specific income level, and their dependents
- Every person aged 70 or over
- Others with specific disease conditions, including some cancers

Hospital cover

At present everyone is entitled to hospital inpatient services in a public ward in all public hospitals. There is a €55 a night charge up to a maximum of €550 in any 12 consecutive months. These charges do not apply to medical card holders. Higher rates apply for semi-private or private care.

⁶⁴ Dr. Owen Smyth, Our Lady's Hospital for Sick Children, Dublin.

Outpatient cover

Attendance at the outpatients or Accident & Emergency (A&E) department of a public hospital, without referral by a General Practitioner (GP), may be charged at €55. There is no charge if referred by a GP. This charge does not apply to those with medical cards, or to those admitted to hospital as a result of attending the A&E department.

Drugs Payment Scheme

Under the Drugs Payment Scheme (DPS) every citizen pays a maximum of €85 each month to cover the cost of prescribed drugs, medicines and appliances. The €85 limit applies to the total drug payments per household (i.e. spouses and dependant children). All costs above this amount are paid by the state.

Private Healthcare Cover

Private health insurance is used to pay for private care in hospitals (or as an outpatient in certain circumstances) or from various specialists in hospitals or in their practices. This is available through the state company Voluntary Health Insurance (VHI) and all employers provide the option of 'Group' insurance cover which has an additional cost benefit. All payments are also deductible from income tax.

In recent years other private health care insurance companies such as BUPA (Ireland) and others have also offered this service. They provide cover for day care/inpatient treatment and hospital outpatient treatment. Payments are fully tax deductible and subscribers can pay for whatever level of hospital care they choose.

Other forms of assistance, such as Disability allowance, also apply in particular circumstances.

4.2.5 Economic aspects

No specific study of the cost benefit of the use of TPMT testing could be found and the view of those consulted was that no such study has been conducted in Ireland because of the low cost of the drug and the relatively low prevalence of the disease (i.e. 30-32 children per year).

An approximate calculation of benefit could be done as follows: It seems that approximately 90% of the population have normal to high TPMT activity, and up to approx 10% are at risk from 6-MP therapy. Therefore the cost of testing 10 samples to find the single patient low in TPMT concentration is approx. € 500 (using the enzymatic assay) or €2500(using a genetic assay). Given that the information obtained is relevant both for avoidance of adverse affects, and also for individualising dosage, this must considered to be highly cost effective.

Figures for 2003 from Dept of Health show the cost of treatments (and length of stay) of Leukaemia patients (table 18). No separate data is available for Acute Lymphatic Leukaemia. However, note that chemotherapy is undertaken in 43% of leukaemia cases (table 19).

Table 18 *Costs of Treatment and Length of Stay for Leukaemia Patients in Irish Hospitals 2003* ⁶⁵

AR DRG	Description	All Inpatient Cases	Average Length of Stay	Inpatient Cost per Case €
R60A	ACUTE LEUKAEMIA + CCC	103	26.45	49,295
R60B	ACUTE LEUKAEMIA + SCC	210	11.15	22,628
R60C	ACUTE LEUKAEMIA - CCCC	545	9.83	8,233

Table 19 *Percentage of Cancer Patients and Types of Treatment*

Table 1.5 Percentage of cancer patients having treatment (numbers do not add to 100% as many patients had more than one treatment type)

	NO TREATMENT	SURGERY	RADIOTHERAPY	CHEMOTHERAPY	HORMONE
colorectal	18%	78%	9%	23%	
female breast	5%	83%	39%	44%	41%
lung	50%	15%	29%	14%	
prostate	24%	54%	5%		34%
lymphoma	22%	15%	18%	63%	
stomach	50%	44%	4%	8%	
leukaemia	57%	2%		43%	
melanoma	6%	93%	2%	4%	

The major drugs of relevance to this study are Mercaptopurine and Azathioprine. The major branded product in use in Ireland is Puri-nethol (Glaxo SmithKline). There are unconfirmed reports that Imuran (Azathioprine) may also be used. Both of these are approved by IMB (table 20).

⁶⁵ Source: Casemix Unit; Dept. of Health & Children

Table 20 Irish Medicines Board approvals of TPMT related drugs

Trade Name	Licence Holder	Licence No.	Strength	Dosage Form
PURI-NETHOL	GlaxoSmithKline (Ireland) Ltd	PA1077/077/001	50mg	Tablets
IMURAN	PCO Manufacturing Ltd.	PPA0465/077/001A	25mg	Tablets
IMURAN	PCO Manufacturing Ltd.	PPA0465/077/002A	50mg	Tablets
IMURAN	PCO Manufacturing Ltd.	PPA0465/077/001B	25mg	Tablets
IMURAN	PCO Manufacturing Ltd.	PPA0465/077/002B	50mg	Tablets
IMURAN	GlaxoSmithKline (Ireland) Ltd	PA1077/059/003	50mg	Tablets
IMURAN	GlaxoSmithKline (Ireland) Ltd	PA1077/059/003	50mg	Tablets
IMURAN	GlaxoSmithKline (Ireland) Ltd	PA1077/059/001	50mg Mg/ML.	Pdr for Soln Inj/Inf
IMURAN	GlaxoSmithKline (Ireland) Ltd	PA1077/059/002	25 Mg	Tablets

Both of these compounds are off-patent products, and therefore open to generic competition.

As an indication of cost, the Glaxo SmithKline indicated product for ALL is Puri-Nethol (Mercaptopurine) and the cost is:

- 100 pack of 25 mg. Tablets: €53.42
- 100 pack of 50 mg. Tablets: €81.29

Glaxo SmithKline also manufacture IMURAN (Azathioprine), which is an immunosuppressant used for several indications, including suppression of the immune system in patients who have had kidney transplants. Although not indicated for ALL, it may be used for treatment of this condition. Azathioprine costs: 100 tabs x 50 mg : €85 in a generic formulation, or €125 for a branded product.

Although Puri-Nethol has limited use, Azathioprine has a wide usage as an immuno-suppressant. In Ireland it is No. 92 in the top 100 drugs covered in the General Medical Service payments list. There were 25,266 prescriptions written for medical cardholders in Ireland in 2002⁶⁶. Obviously there are many more for patients covered by private health insurance.

An interview with GSK (Ireland) failed to elicit any information on trends in Puri-Nethol, or the impact of TPMT testing on its sales. As an ‘old’ product with a very low patient base, the product sales in Ireland are no longer tracked by the company. There is no product manager and the product is not specifically promoted to clinicians.

They were therefore unable to comment on any impact of drug use resulting from the use of patient screening.

4.2.6 Social aspects: patients’ attitudes

No issues of a social or ethical nature arose during the discussions with clinicians or others. Given the nature of the disease, there is no resistance to the testing protocol and questions about the nature or purpose of testing are rare. The nature of the TPMT test is phenotypic and there is therefore no requirement for specific patient consent in taking the sample. If genetic tests are introduced, this may change.

The major legal issue in this area would appear to be the clinicians’ motivation to avoid malpractice actions by ensuring that any possible pre-screening that may avoid adverse reactions is conducted. TPMT is clearly a case where it is prudent to ensure that all patients are pre-screened.

Interviews

1 representative from:	Dept of Health & Children
1 representative from:	Dublin Molecular Medicine Centre
2 representatives from:	Irish Medicines Board
Panel views from:	Irish Cancer Society patient helpline
1 representative from:	Irish Insurance Federation
3 representatives:	Hospital Clinical Laboratories involved in Her2 testing
1:	Consultant Oncologist
2:	Representatives of Dako and Roche (Ireland)

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⁶⁶ See reference 4.

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4.3 TPMT testing in the Netherlands

4.3.1 Historical overview

Treatment of children with ALL

In the Netherlands, approximately 100 children per year are diagnosed with Acute Lymphoblastic Leukemia. All children are treated in centres for pediatric hematology and oncology. In total, there are 6 of these specialized centres in the Netherlands.

All children are treated according to protocols of the Dutch Childhood Oncology Group (DCOG), in most instances international protocols. After a heavy pre-treatment the children are given a maintenance therapy with low doses of 6MP and MTX.

TPMT testing

TPMT testing in children with ALL was introduced in the Netherlands after extensive basic research in lymphoblastic cell lines and clinical research in the biochemical pharmacology of 6MP and MTX and purine and pyrimidine metabolism in lymphoblastic leukemia in the Department of Pediatric Oncology in Nijmegen since 1980. Financial support for the research was provided through the Dutch Cancer Society. From 1997 until 2000 TPMT levels of all children in the Netherlands with ALL was measured several times during their treatment with 6MP. Blood was sampled at diagnosis and during maintenance treatment. Blood was screened for most of the known mutations in the TPMT-gene and the prevalence of these mutations was compared with controls not suffering from haematological, immunological and nephrological diseases. Methods described by Yates et al were used, with some modifications. The Nijmegen laboratory also conducted studies in adult patients with rheumatological diseases treated with Azathioprine. However, after finishing these research projects, standard testing is not conducted anymore.

In recent years, the Nijmegen laboratory introduced a validated molecular genetic test which screens for mutant alleles associated with TPMT deficiency. This is a home made test. In addition, direct (phenotypic) measures of enzymatic activity is still available, which is also home-made.

To date, testing on TPMT deficiency is centralized. The laboratory in Nijmegen is the only laboratory in the Netherlands that offers testing on TPMT deficiency, either by an enzyme test and more recently also by DNA testing.

The heads of the laboratories see advantages of DNA testing above enzyme testing, especially because blood transfusions during therapy can increase the TPMT activity in TPMT deficiency or in heterozygous patient because of a mixture with the higher donor erythrocytes.

4.3.2 TPMT test and clinical practice

Currently, all children with ALL are treated according to the DCOG-ALL-10 protocol. After a heavy pre-treatment period the children are given a maintenance therapy with low doses of 6MP (50 mg/m²). Along with the treatment is weekly or two-weekly measurement of leukocyte and trombocyte status.

Based on this, the dose of 6MP will be monitored and reduced or increased if necessary. This protocol does not include standard testing for TPMT deficiency before start of the treatment. However, it is recommended to test for TPMT deficiency in case of severe or persistent hemotoxicity. In the DCOG-ALL-10 protocol it is mentioned that physicians request the laboratory from Nijmegen to conduct TPMT testing.

The lab in Nijmegen receives several requests per year to conduct such a test. Up till now, an enzyme test is conducted, however genotype testing is available.

This can be more advantageous, because an important drawback of phenotyping is that thiopurine drugs can stimulate an increase in the patient's TPMT levels in comparison to the TPMT level at diagnosis. In addition, DNA testing is preferred because of blood transfusions can give a non valid TPMT level, mixed with the activity of donor erythrocytes.

To facilitate DNA testing, the organisation of the molecular lab in Nijmegen has conducted several changes. In particular, the time from testing to presenting results has been changed dramatically. It now only takes a week to receive the results (in general, genetic tests take much more time).

Although physicians from several hospitals and lab workers from the biochemical and from the molecular laboratory in the Nijmegen hospital clearly see advantages of implementing the test on a routine basis for all ALL patients, also many barriers were mentioned.

Barriers for not implementing the test

Various different reasons were mentioned to explain the lack of testing in the standard treatment for children with ALL. The most important reason mentioned by physicians for not introducing TPMT testing is the lack of perceived benefit. "there is no one who really

feels such a benefit to introduce TPMT-testing for all children with ALL". They don't see a perceived benefit in several ways. The first is that there will always be toxicity during treatment for these patients.

In fact, aim of the treatment is to reach toxicity (in tumour cells). They reason that children with ALL suffer in any way from toxicity. Therefore, toxicity is more easily accepted in these patients. Also a member of the "Foundation of parents with a child with cancer" shared this vision. However, all interviewed physicians and laboratory clinicians thought it could be very different for other groups of patients, e.g. patients with rheumatoid arthritis, where toxicity is intolerable.

Secondly, only a small part of toxicity is caused by TPMT deficiency. There are many other reasons for myelosuppression following 6MP use, suggesting that such tests on their own are not enough to replace the existing requirement for weekly blood measurements for those receiving thiopurine drugs.

Finally, only for a very small group of children under treatment, the 6MP dose would change at forehand when you should know their TPMT status. Of course for the wild type group, nothing would change. However, also for the heterozygote patients nothing would change, because decreased TPMT activity does not completely predict toxicity. Thus, the normal dose would be tried and reductions would be made if necessary.

Thus, only the 0,3% of children with a homozygote TPMT deficiency would benefit from predictive testing. In the Netherlands, this is about 1 child in three years.

An important reason mentioned by the lab specialist (from the biochemical and from the molecular laboratory) is the lack of knowledge in physicians with TPMT deficiency itself and with the availability of the TPMT test. There is no standard way of informing or educating the physicians. Up till now, the heads of the biochemical and molecular laboratories inform the physicians by organizing lectures and by giving presentations during (international) conferences.

In addition, interpretation of test results has been made easier by describing clearly the conclusions of the test results on the same paper. However, there is no structural way of knowledge diffusion. The last reason mentioned for not using a test was the unclear reimbursement situation. It is not clear how these tests can be reimbursed properly.

Advantages mentioned for introducing the test were the benefits for the individual child with homozygote TPMT deficiency. "of course the individual child with clear TPMT deficiency would benefit, however this is only a very small number of the children treated for ALL". Interestingly, there is no lack of testing for organisational reasons. Blood of all children with ALL is centrally stored for research and could be used for predictive testing. One physician mentioned that although testing would be more relevant in other diseases (rheumatoid arthritis) the organization to test these patients would be far more difficult. In addition, costs were not mentioned as an important barrier. Treatment of these patients is already expensive. One extra test is not really an obstacle.

4.3.3 Quality aspects

The quality of the tests are guaranteed by the normal quality system for laboratories. Quality of the enzyme and DNA test are within the normal accreditation system, (CCKL accreditation). There is no special quality assurance scheme for these tests.

4.3.4 Approval and reimbursement

Reimbursement of medicines and tests is regulated by College Tarieven Gezondheidszorg (CTG). Because there are such a few tests conducted, no separate reimbursement system for TPMT tests is developed yet. There are discussions with the CTG to introduce a separate system for pharmacogenetic tests, but this has not been finalized. Currently, these tests are categorized within postnatal genotyping. (645 Euro per test). However, the costs for these tests are paid through the hospital budget.

Because only a few tests per year are conducted, the costs per test are actually more than necessary.

4.3.5 Economic aspects

No cost-benefit analysis in the Netherlands has been done. Because the use of the test is very rare, no financial effects have been noticed within the concerned pharmaceutical companies. In addition, when testing would be done on a regular base, still the number of children who would not receive initial treatment on basis of the test results will be very small. In the current situation, also treatments are reduced in case of toxicity.

4.3.6 Social aspects: patients' attitudes

Until now, no specific concern was seen with regard to informed consent. Parents are asked for informed consent before the test is conducted (which is indeed very seldom), and this has never been a problem. As far as the physicians remembered, no one ever refused the test. In the opinion of the physicians and the member of the VOKK, the genetic basis of poor treatment metabolism is of no particular concern to the parents. These parents have already to deal with a life threatening disease with many tests and medical procedures.

This test is been seen as one of the many tests the child has to go through. Before the test has been conducted, no problems in informed consent have been mentioned until now. In addition, physicians saw not problems in presenting the results of the test. Parents want to know what causes the toxicity and seem relieved that the cause has been found. In fact, the nature of the test seems not to play any specific role.

This might also be caused by the fact the TPMT deficiency has no other effect on children's further functioning in life. It is only related to the specific treatment for a specific disease and has no further implications for life. It is more or less seen as the same as the assessment of the coagulation status before giving anticoagulantia. No one saw any reason to test other family members of a child with a TPMT deficiency. The usefulness of such a procedure was not seen.

Further information.

Although the testing on TPMT in childhood leukaemia is not yet recommended, testing on TPT deficiency in other diseases is seen as more advantageous in order to avoid unnecessary toxicity.

Interviews:

2 interviews with laboratories
3 interviews with physicians
1 interview with patient organisation
1 interview with health care insurance

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4.4 UK case study: TPMT testing with ALL

4.4.1 Historical background

This case study focuses on the use of a diagnostic test to ascertain TPMT activity prior to prescription of the drug 6-mercaptopurine (6-MP), brand name Puri-Nethol, for the treatment of childhood Acute Lymphoblastic Leukaemia (ALL) within the UK. The treatment of leukaemia is the only approved indication for 6-MP and it is not used beyond leukaemia in the UK at the present time, although it may also be useful for the treatment of Inflammatory Bowel Disease (consultant haematologist 1).⁶⁷

The incidence of ALL in the UK is 4 per 100,000 per year, which equates to around 450 cases per year, with a median age at onset of 3-7 years.⁶⁸ ALL is the most common

⁶⁷ See <http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=763#CONTRAINDICATIONS> accessed 01/04/05.

⁶⁸ www.lrf.org accessed 01/04/05

childhood cancer in the UK, but the majority of patients are able to survive the disease.⁶⁹ The therapeutic regime, which lasts around two years for girls and up to three years for boys, is associated with a significant risk due to the toxicity of the drugs involved (consultant haematologist 1). One important toxicological risk comes from 6-MP, which is a major component of the treatment regime in the UK and is poorly metabolised by some members of the population. The current medicine datasheet for 6MP carries the following information relevant to adverse events related to metabolism of the drug:

‘There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of 6-mercaptopurine and prone to developing rapid bone marrow depression following the initiation of treatment with Puri-Nethol. This problem could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulphasalazine. Some laboratories offer testing for TPMT deficiency, although these tests have not been shown to identify all patients at risk of severe toxicity. Therefore close monitoring of blood counts is still necessary.’⁷⁰

Azathioprine, a pro-drug that is effectively a slow release version of 6-MP and widely used for a range of diseases in the UK is not used for leukaemia treatment in the UK (personal communication UK pharmacist 3). Thioguanine, another drug in the same family as 6-MP has been associated with greater levels of liver toxicity and is used more sparingly (consultant haematologist 1). Although TPMT testing is increasingly practiced prior to prescription of thiopurine drugs for conditions other than ALL in the UK (lab1, lab2, lab3) this case study focuses primarily on the use of the test in patients with ALL.

At the start of the 1980s, a consultant haematologist’s interest at Sheffield’s Royal Hallamshire Hospital drove the investigation of drug metabolism in the treatment of patients with leukemia and other disorders receiving thiopurine drugs following the observation that some patients did not benefit from treatment at all while others did (lab 2). This clinical interest supported and encouraged successive post-doctoral biochemistry research projects at the University of Sheffield. The initially research focused on measures of drug metabolites in patients to predict adverse events, possible as thiopurine drug metabolites accumulate within cells. The investigator’s choice of red blood cells for analysis represented an unusual methodology at the time and peer acceptance was difficult to obtain. This was because it was the norm for plasma (or serum) to be analysed for drug metabolites and nobody looked at drug concentrations within cells. However the researchers showed that red cells could be used as a surrogate tissue. The choice of red blood cells was thought to be more logical as these required less blood (2ml vs 20ml) be drawn from the patient (often a sick child).

Financial support for the research was ultimately provided through a combination of local charity research grants and research council support, but at times it was difficult to

⁶⁹ according to patient information leaflet for ALL2003 trial available at:
http://www.cts.uox.ac.uk/projects/ukall2003/UKALL2003v3_parent_info.doc accessed 01/04/05

⁷⁰ See <http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=763#CONTRAINDICATIONS> accessed 01/04/05.

sustain the research (lab2). At around the same time in the USA, research by Richard Weinshilboum at the Mayo Clinic (Rochester, MI) resulted in the isolation of the TPMT enzyme and its association with metabolism of thiopurine drugs (Weishilboum et al 1980). Collaboration with Weinshilboum at the Mayo Clinic allowed the Sheffield group to demonstrate that TPMT was an important enzyme in the metabolic pathway for thiopurine drugs (Lennard et al 1987). Weishilboum's work ultimately led to the cloning of the gene for TPMT in the mid 1990s, and the elucidation of the TPMT enzyme's DNA sequence and amino acid sequence. This allowed the clinical observation of adverse reactions to be directly related to mutations in the TPMT gene and the formulation of a DNA test for a number of relatively prevalent specific mutations followed (lab1). This avenue of research took around a decade, which is apparently not unusual (lab2).

In recent years UK laboratories together with those overseas have developed a number of distinct methods for determining the TPMT status of patients using both biochemical tests and molecular genetic tests. Indeed each laboratory in the UK currently use their own distinct methods primarily based on the type of resources, such as instrumentation systems, and skills available locally.

4.4.2 TPMT testing and clinical practice

Testing methodologies

The basic molecular genetic testing methodology developed in the mid 1990s for detection of mutations associated with TPMT deficiency utilises PCR combined with restriction enzyme digests to manually to detect the presence or absence of a specific DNA sequence at a known loci (Yates et al 1997).

A molecular genetic test that focuses of the most common mutations is relatively inexpensive (around £20-30) but would only pick up about 90% of mutations in the Caucasian population (lab2). The Asian population have a similar range of mutations to Caucasians, but at lower incidence (lab 2) and there is some evidence to suggest that the Afro-Caribbean population have a higher incidence and some distinct mutations (lab 3) and so it seems that a molecular genetic test using a limited panel of mutations must be validated for the population for which it is used. The heterogeneity of the UK population as a whole and the possibility of rare or even unique mutations that might affect a patient's observed metabolic activity for the TPMT enzyme mean that current molecular genetic techniques are not the preferred option for clinical testing at present for ALL (consultant haematologist 1) or TPMT testing as used more generally (lab3).

The more common methodologies for TPMT testing used in the UK at present are based on direct (phenotypic) measures of enzymatic activity, based on the rate at which the enzyme extracted from patient's blood cells can metabolise a thiopurine substrate under laboratory conditions. Once the enzyme incubation is complete a range of methods may be employed to separate out and measure the relative quantities of substrate and metabolites including radiometric assays, high pressure liquid chromatography combined with fluorimetric measurement, and tandem mass spectroscopy (labs 1-3). There does not seem to be any consensus at present over the superiority of any one method and users

emphasis the advantages of their own techniques as would be expected. Nonetheless phenotypic testing methodologies do share common advantages over molecular genetic testing methods although they also share some disadvantages too.

Provided the assay is devised correctly the full range of enzyme activity that exists in a population can be observed in a quantitative manner (lab 3). A recent population study of over 1000 randomly selected individuals' TPMT activities in the UK population demonstrated that a normal distribution for TPMT activity may be observed rather than a trimodal distribution that might be expected from a simple distribution that arises from a gene that is either working or not working, and thus a 'right tail' on a statistical distribution showing enzyme activity can be observed indicating the existence of hyper metabolisers as well as a number of individuals deficient for TPMT activity (Ford et al 2004a). Whereas in low metabolisers the drug's metabolites built up to toxic levels, in high metabolisers they were cleared too effectively, although this subtlety of usage is reportedly less commonly known by users of some the TPMT testing services available in the UK (lab1).

Thus a test could be used to inform a physician to increase their dosage of the thiopurine drugs during treatment. In this manner, a phenotypic technique allows for the tailoring of dosages for the full spectrum of patients rather than just low metabolisers as the molecular genetic test might. This could potentially mean that a much higher number of patients than the 1 in 300 expected TPMT deficient patient could benefit from phenotypic testing (lab1, lab3).

Furthermore the equipment used for phenotyping can also be used to detect the build up of drug metabolites in patients' red blood cells once they have initiated their therapy thereby allowing physicians to tell whether patients are complying with the therapeutic regime. This is particularly useful as compliance is apparently a problem in around 10% of child patients (lab2, consultant haematologist 2).

An important drawback of phenotyping is that thiopurine drugs can stimulate an increase in the patient's TPMT levels. In some circumstances this would make it necessary to test the patient prior to commencing their thiopurine treatment to get the most accurate indication of baseline TPMT activity (lab 3). However in the case of ALL TPMT activity at disease diagnosis does not give an accurate indication because the anaemia associated with ALL produces a downward shift in TPMT activities. Although those with extreme TPMT activities can be determined, heterozygote activity in ALL suffers is best determined by phenotypic testing once they are on maintenance therapy. This does not apply to patients taking azathioprine, or adults taking 6MP as an immunosuppressive. Basal activity can be accurately predicted prior to the start of drug treatment. TPMT activity does not change during low dose immunosuppressive therapy (lab 2).

Another drawback is that the unreported use of blood transfusions can create a misleading impression of the patient's metabolic ability (Ford et al 2004b).

Further problems related to the perceived technical complexity of assays have led to difficulties in establishing testing more widely (lab 3) as well as inhibiting the reproducibility of results even from the same sample in different labs – perhaps because of differences in the quality of thiopurine substrate supplied by manufacturers (Oh et al 2004). However, it seems that these disadvantages mainly reflect the need to address organisational issues within the therapeutic regime or quality control issues in the laboratory rather than being insurmountable technical obstacles.

Despite the profusion of potential tests to predict patient response to thiopurine drugs, there are limits to the utility of both phenotypic and genotypic measures available. For example in some cases it has been reported that individuals can ‘bounce’ between ‘normal’ and ‘low’ ranges when tested on different occasions – a phenomenon that has no clear genotypic basis (lab3). Indeed it is suggested that TPMT activity may be caused to vary by a variety of factors including diet (lab1, Oh et al 2004). Furthermore Winter et al (2004) suggest that only 29-50% of cases myelosuppression following Azathaprine use may be accounted for by TPMT deficiency suggesting that such tests on their own are not sufficiently robust to replace the existing requirement for weekly red blood cell counts for those receiving thiopurine drugs.

Nonetheless while RBC represents a post-hoc measure of drug toxicity, predictive tests are the only way to ensure that a patient commences therapy at a suitable level. As such these tests have found some application.

As techniques for TPMT testing developed through the 1990s, a limited local service was offered from Sheffield on the back of research grants. A London hospital-based laboratory also commenced a service for TPMT testing in the early 1990s and a third laboratory in Birmingham has joined them in the last couple of years.

However the London and Birmingham laboratories do not provide a service for ALL patients, due to a special circumstance arising from national scale clinical trials for leukaemia currently ongoing in the UK. These trials, known as UKALL 1997 and UKALL 2003 (reflecting the year in which they commenced) utilised the phenotypic test developed in Sheffield. The uptake of the test as part of the trial protocol was facilitated partially because the clinicians who worked with the laboratory researchers previously were involved in the organisation of the trial and championed the inclusion of the TPMT test as part of the ‘package’ of projects associated with the trials.

The main objective of the ALL trial that commenced in 1997 was to determine whether 6MP or thioguanine was a more effective drug for the treatment of ALL while the main objective of the ongoing UKALL 2003 is to assess the effect of different intensities of drug treatment over the course of a patients’ therapy. A subsidiary question of the UKALL 1997 trial was to assess whether genotypic or phenotypic testing provided a more accurate picture of patient drug response. The results from the UKALL 1997 trial, which ended in 2002, have yet to be released and the analysis is ongoing (lab2).

At the present time the laboratory associated with the UKALL 2003 trial remains the only laboratory offering a service for ALL patients in the UK (lab1, lab2, lab3).

Clinical practice

As previously stated phenotypic TPMT testing using a biochemical assay is undertaken in the UK as part of a research programme based around national scale clinical trials for the treatment of ALL. Neither the NHS nor the drug manufacture has played any significant role in the bringing about this widespread application of the test. Instead the Medical Research Council fund the trial and the Leukaemia Research Fund support the laboratory providing the trial with the phenotyping tests (charity 1, lab2, consultant haematologist 1).

Every ALL patient in the UK is offered the opportunity to join the trial and it is clear that the vast majority appear to do so as between 350-400 children affected by ALL join the trial each year. A total of 1900 patients were enrolled in UKALL 1997 and around 2300 are expected to join UKALL 2003 (lab2).⁷¹

The use of the TPMT test in the clinical setting is suggested to be straightforward and non problematic (consultant haematologist 1 and 2, pharmacist 1 and 2). At diagnosis a blood sample from those patients joining the trial is sent to the trial laboratory. However the total volume of tests conducted by the trial laboratory is much higher than the annual number of new patients.

This is because metabolite testing for patient compliance (i.e. to detect whether the children are taking their medicine) is also undertaken, and some genotyping is undertaken (indeed a direct comparison of the phenotyping and genotyping tests was a particular feature of the UKALL 1997). In total the laboratory conducts an estimated 2000 tests for the trial per year of which around 600-700 tests could be considered pharmacogenetic tests rather than metabolite tests.

The clinical users of the ALL TPMT testing are haematologists and their supporting nursing and pharmacist staff in 21 centres throughout UK where treatment for ALL is focused.

Due to the complexity of the biochemical assaying technique employed the trial lab typically take three days to process a batch of around 25 samples (lab 2), however the test results may take as long as three weeks after sampling to arrive with the physician (consultant haematologist 2).

This does not impede the present protocol as the 6MP treatment does not commence until around four weeks into the programme (consultant haematologist 2). The metabolite testing is also often slow to be returned, and can take 6-8 weeks which would mean it would not have a high utility if this were to become a clinical service (consultant haematologist 3). These time scales could be reduced dramatically (as shown by the

⁷¹ See also the patient information leaflet for ALL2003 trial available at:
http://www.ctsu.ox.ac.uk/projects/ukall2003/UKALL2003v3_parent_info.doc accessed 01/04/05

activities of other TPMT testing labs). However the trial lab is not adequately resourced for high turnaround and processes samples in batches (lab 2).

Test results of concern are generally communicated by telephone as well as in writing from the laboratory to the department where the patient is being treated. A deficient metaboliser will have their 6MP dosage capped from the start of the trial (pharmacist 2). Prescribing is a team activity involving nurses, doctors, and pharmacists and results are shared and used as one of several sources of information when considering a patient's dosaging strategy (pharmacist 1, 2). Most patients can be treated as outpatients and when returning for a weekly monitoring appointment, blood is taken for a RBC.

Although the RBC is a crude measure of 6MPs effect on the cancer because many factors affect RBC, the procedure is well established and high RBCs are correlated with a poor prognosis (haematologist 2). The RBC procedure is automated and highly robust, providing a clinician with a result within an hour at most, while the patient is waiting, thus the consultation, dosage adjustment and drug dispensing can all be achieved in one visit (pharmacist 2).

Potential barriers to routine use

The use of TPMT testing for ALL in the UK has been described as on the threshold of moving from a research test to a service test because although widely used, at present it is not funded by the NHS (consultant haematologist 1). However cost is not seen as too much of an obstacle by users as the test is not particularly expensive and individual departments only see 10-40 cases of ALL per year.

This cost is seen as relatively small given that the NHS already spends many thousands of pounds per year treating each ALL patient at present (consultant haematologist 2), although laboratory reports suggest this may not be the view point of other medical specialities where costs and benefits of the testing process are not as well aligned (lab 1). We return to this point in section 5.

The test is apparently relatively easily integrated into existing practice as noted previously. However while some clinicians seemed to think uptake of the test was very high in the ALL trial, in fact other clinicians and the laboratory indicate that a significant proportion of departments did not fully comply with the guidelines for sending samples before prescribing TPMT, despite the test being freely available at the present time and part of the required trial protocol. Indeed this is not peculiar to the ALL trial, and taking TPMT testing in the UK as a whole it seems that regrettably, the diligence of some physicians is only guaranteed after close experience of adverse reactions (labs 1-3). However one possible reason for non-compliance of physicians was cited as being the length and complexity of the trial documentation - with the testing protocol buried on page 60.

Another explanation may be that physicians with a good knowledge of the trial protocol are not solely responsible for the delivery of samples to the laboratory. Indeed sometimes a physician may have to rely on staff at another institution to take a sample (consultant haematologist 3). Education of the users, be they physicians or other staff members is

therefore a another potential hurdle. The trend in the UK is towards the increasing use of a higher division of labour with nurses and pharmacists being given roles as supplementary prescribers. These professionals also need to be educated in the use of PGx tests. It is questionable whether these professionals would be willing or able to take on these additional responsibilities (pharmacist 2). On the other hand having a dedicated member of more junior staff whose duty it is to collect such samples is reportedly helpful, as occurs in one institution where a research nurse was employed (consultant haematologist 3). This is useful because the low volume of ALL patients seen by most departments mean that many staff will be unfamiliar with the full details of the trial protocol (consultant haematologist 3).

The nature of ALL treatment means that often patients will be given blood transfusions, perhaps before they join the trial, and in these circumstances it may be difficult to accurately undertake TPMT testing using the phenotypic test, as mentioned previously. However, the genotypic test is available in the trial laboratory so that these patients can receive this test if more suitable, but unless staff understands the importance of informing the relevant person about the transfusion then the laboratory would not know they might be supplying an invalid result (consultant haematologist 3).

Although it appears some sites have had problems ensuring samples are collected at the right times in their early days using the test (consultant haematologist 3), overall the wide scale adoption of TPMT testing seems to have occurred with relative ease. However this is likely to be due to the strict rules of the trial protocol. Diffusion in TPMT testing in other areas of medicine appears to be more difficult, although some specialities such as dermatologists and gastroenterologists are reportedly more accepting than others (lab 1, lab 3).

Apart from the clinical issues in technical terms the test itself is cumbersome and difficult to establish for new users. Where new labs are required to offer a service in the UK or in other countries, the difficulties of the assay may hamper diffusion. In particular the assays currently used are 'home brews', dependent on substrates that have been problematic to obtain in some cases (lab 3) Only in one case is the assay used EC kite marked.

Another issue at present is the time it takes to conduct a test – the biochemical assays used at present for the majority of tests undertaken in the UK are time consuming taking 2-3 days (lab1, lab 2), although careful optimisation can reduce this time (lab3). It is possible that commercial interest may allow the development of chemistries to facilitate rapid tests and perhaps even near-patient tests that could show a result with a colour change (lab2) but whether near patient methodologies would be capable of providing fully quantitative information is not known (lab3).

Already US companies (especially Prometheus)⁷² have developed a series of tests for TPMT activity (genotype, enzyme activity and metabolise screening) which they offer as

⁷²See <http://www.prometheuslabs.com/212a.asp?nav=products> accessed 23/01/05

a service, although the relative strengths and weaknesses of the methods they employ have not been investigated here.

The move from the complex and slow biochemical techniques used at present to fully automated, high throughput tests on dedicated commercial chemical pathology autoanalysers is possible in principle but this is only feasible once the clinical parameters are more fully characterised as a result of the knowledge base maturing. This is thought likely to take a few more years (at least 5) for TPMT, and even when this has occurred, translation into autoanalyser chemistry and development of a commercial kit may take another 5 years (lab 3). It is therefore possible that the move from initial scientific observation to rapid routinised test could be as much as 30 years.

In the meanwhile, testing is conducted on instrumentation designed for research use. These machines are “not meant to be hammered 24 hours a day” (lab2) and breakdowns can be a problem. Each sample is assayed in duplicate, and each assay takes 15 minutes to run through the HPLC. Together with quality control samples and cleaning cycles 25 patient samples may take more than 24 hours to run using some methodologies – although other labs report faster methods.

Although research is proposed that would allow a comparison of the efficiency of biochemical assays of 6MP metabolism testing versus RBCs, until these tests can provide answers in the same timeframe as RBCs, (i.e. within an hour), their utility will be limited, or will entail disruption to existing practice that might require new methods of drug monitoring to be found (consultant haematologist 2, pharmacist 2). It is also worth mentioning that although a delay of several weeks for a test result is acceptable given its position within the ALL trial regime (where the test is undertaken at diagnosis and 6MP treatment commenced after several weeks) for other areas of medicine this waiting time might limit the utility of the test. This has forced at least one other laboratory to guarantee processing and reporting in five days (lab 3).

4.4.3 Quality aspects

A distinction must be made here between the regime governing quality of TPMT testing provided within the UKALL clinical trials - a research programme that happens to be available nationally and takes in almost all ALL patients, and the regime that is in place for the governance of NHS testing services, including those laboratories that offer TPMT testing for clinicians treating other conditions where thiopurines are used, but excluding ALL. Since the ALL clinical trials are research projects that do not involve NHS laboratories, the service is not provided by an accredited laboratory, nor are the relevant staff currently involved in a quality assurance scheme, although investigations into the membership of such a scheme have been made.

Should TPMT testing for ALL be accepted as a routine procedure within the NHS, it would be appropriate for the laboratories involved in providing that service to sign up to the existing TPMT quality assurance scheme recently established by an NHS laboratory (lab 3).

4.4.4 Economic aspects

The economic aspects of TPMT testing are discussed here include (i) the cost-effectiveness of TPMT testing for the NHS (ii) the reimbursement for TPMT test healthcare providers (iii) the economic impact of TPMT testing on the sales and marketing of thiopurine drugs.

(i) Cost effectiveness of TPMT testing

No studies have been reported to date that focus on the cost effectiveness of TPMT testing for ALL in the UK (lab2) although studies of TPMT testing as used with Azathioprine for inflammatory bowel disease do demonstrate its cost effectiveness (Winter et al 2004). At least one other author interviewed on TPMT testing seem convinced that the test is cost effectiveness for all thiopurine drug use given the high cost of a death in QALYs versus the cost of testing, saying “it is a no brainer”.

The results of the ALL trials are likely to answer cost-benefit questions for a number of related factors in the treatment of ALL. The results will not be complete for 2 years. However as the test is not charged for at present, and is not officially used and it is unlikely that clinicians or departments involved in the treatment of ALL have undertaken such work at this stage, although some are still convinced of its cost effectiveness (consultant haematologist 2). It has been suggested that for clinicians using 6MP and Azathioprine for a range of conditions, a primary motivational factor for becoming a TPMT service users is the occurrence of a serious adverse event in their clinic as a result of not testing, as mentioned previously (lab1, lab2, lab3). However, a departmental level cost-benefit analysis might be expected to show that for the treatment of some conditions the costs and benefits of testing accrue to different departments – thus potentially making TPMT testing financially unattractive at the user level, even when it may be cost-effective at the NHS level or whole societal level (lab 1, DoH1).

(ii) Reimbursement for TPMT testing

The National Health Service provides healthcare that is available for all and is free at the point of use. As such the NHS is the major reimbursor of healthcare costs within the UK. However at the present time the TPMT testing for ALL undertaken in the UK is funded by the Leukaemia Research Fund as part of the UKALL 2003 clinical trial. This funding is expected to continue until 2007, although it is expected to cease thereafter as after 10 years support, the LRF feel the test should be adopted by the NHS and the LRF are hopeful that they will do so (charity 1). At present the NHS does not pay for any TPMT testing associated with ALL although, TPMT testing is reimbursed with NHS funds at other UK laboratories serving client physicians who prescribe Azathioprine. Indeed the refinement of testing methodologies has led to a fall in the price of such tests over recent years, and services are now available for £25-40 (lab1, lab2, lab3).

Reimbursement for testing services like TPMT is generally negotiated at the local level as required between the laboratory and the client department. The Department of Health would be unlikely to intervene in this situation unless the testing brought significant financial implications (personal communication – UK Genetic Testing Network).

The largest private health insurer and provident in the UK is BUPA. The perspective provided here does not necessarily reflect the view of BUPA, but was provided by a BUPA employee. BUPA have little demand from their customers for claims surrounding severe illness in children. This is mainly due to the small number of private hospitals due to stringent regulations to ensure child safety and strong NHS provision in the UK. As such they have not needed to consider reimbursement for TPMT testing as related to ALL specifically, and in general it seems that they are not aware of any demand for TPMT testing reimbursement.

Overall BUPA does consider that pharmacogenetic testing has some valuable contributions to make in medicine, but so far these have been slower to emerge than previously expected. The lack of progress in the field to date was felt to reflect more than just the usual slow advancement of medicine. It was noted that genetics is a field that has been particularly susceptible to hype given its political cachet.

(iii) Sales and Marketing implications of TPMT testing

The commercial reality of TPMT testing was concisely summed up by consultant haematologist 1: *"I suppose you could say that there isn't really a financial incentive for the big pharma to become involved in this area"*.

The main thiopurine drug used in ALL treatment, 6MP, is currently marketed under the name puri-nethol by GlaxoSmithKline. The commercial perspective from GSK presented here is based on one employee's view and does not necessarily represent the view of GSK.

Having first been brought to the market in the 1950s, 6MP is now off patent and as such is potentially at risk of generic competition. However, the UK market is relatively small, at around one million pounds per annum, with Azathioprine (marketed as Imuran) worth only marginally more.

No generic competitor has so far been enticed into the UK market. This is thought to be unlikely to change as at the start of 2005 GSK cut the price of 6MP by over 85% from £61 to £7.99 as part of a package of measures to appease the Government's concern over NHS expenditure on pharmaceuticals. Nonetheless generic azathioprine is available. There are a number of UK non-proprietary forms. Available from APS, Ashbourne (Immunoprin), Lennon (Oprisine), Penn (Azamune), and others (lab 2).

It is clear the thiopurine drugs are seen by GSK as relatively low revenue generating products, servicing small and mature markets, with little competition. As such they are not inviting candidates for investment. Indeed GSK allocates negligible resources their sales and marketing at present. It is therefore not surprising that they have not been pursuing the development or marketing of a pharmacogenetic test to support the drug prescription. There is no evidence to suggest that the introduction of TPMT testing by UK laboratories has increased the market for the drug, and given the small size of the market, any marginal impact would be of little consequence to GSK. On the one hand,

the company has been supportive of efforts by research sciences in the field, for example through the donation of thiopurine substrates for the development of assays (lab 3, Ford et al 2004a) However at the same time commercial pressures mean that GSK is withdrawing the smaller tablet size for 6-MP, desirable for dosage tailoring. This has forced the UK trial organisers to look into the possibility of contracting an overseas manufacture to supply tablets in the size they require (consultant haematologist 1).

The firm's (non) strategy for TPMT testing contrasts with GSK's strategy for more profitable drugs such as the HIV therapy Ziagen (Abacavir) which has UK sales of £10-12M. HIV is now regarded as a chronic condition as HIV positive patients can expect to enjoy full lives if their condition is well managed. Ziagen therefore serves a market that is higher profile and larger than that of the thiopurine drugs.

Ziagen is associated with a potentially fatal adverse reaction in around half the white male population (Tucker 2004) and GSK have been more proactive in their use of pharmacogenetics in seeking a solution to address this problem.

4.4.5 Social aspects

In the development of the UKALL clinical trial protocol no special consideration was given to the wider implications of revealing the genetic status of individuals to the families of TPMT deficient patients. This stance did not raise any objection when the research project came before the childhood leukaemia working party (composed mainly of haematologists and oncologists) which over sees all leukaemia trials in the UK, (consultant haematologist 1 & 2). The LRF also has found no cause for concern with this situation (charity 1).

Although the obtaining of informed consent prior to diagnostic testing is considered to be an important principle (lab1), in practice many patients involved in the UKALL clinical trials are not informed of the nature of the TPMT test prior to the procedure and the patient information documents do not contain specific mention of the pharmacogenetic test for TPMT.⁷³ However patients or their parents are asked to sign a consent form for the trial as a whole, including the research projects attached, of which TPMT testing is one (consultant haematologist 1 & 2).

The low priority given to informing patients of the test reflects the view of clinicians and laboratory staff using TPMT testing within the context of the ALL that the genetic basis of poor or deficient thiopurine drug metabolism is not of particular concern to the families of patients who are coping with a life threatening disease as the test is seen as part of the solution to the problem of drug toxicity or ineffectiveness (consultant haematologist 1 & 2, lab 2). At some sites it seems that in general patients are not told about the test unless they are found to be TPMT deficient, but in other sites the family is told (consultant haematologist 3). Either way it seem that when this situation arises in discussion it appears that the test is seen as a good thing because it is helping to resolve the issue of why a potentially life saving drug treatment has become problematic. Indeed in the context of the treatment, which is said to place a huge burden on the family, the

⁷³ See http://www.ctsu.ox.ac.uk/projects/ukall2003/UKALL2003v3_parent_info.doc accessed 01/03/05

genetic implications of the test “play an extremely minor role” (consultant haematologist 1). It is conceded that in any other circumstances a test revealing a genetic characteristic might raise a concern but in this particular context the combination of the life threatening disease and the array of information relayed to families are suggested as reasons as to why further discussion of TPMT testing would not be considered a priority by patients or practitioners (consultant haematologist 1, pharmacist 2).

There is uncertainty about the natural role of the TPMT enzyme (which of course did not evolve to metabolise thiopurine drugs) so the full implications of being deficient are not known (lab1). However, as far as we know - there are no implications of being TPMT deficient unless the individual takes thiopurine drugs.

However the possibility of a family being faced with a recurrence of disease in another family member deficient for TPMT activity is considered remote, but not entirely unfeasible. Nonetheless laboratory staff do not consider the genetic basis of TPMT deficiency should be a significant concern to family members beyond the patient (lab1, lab2, lab3). Overall, there seems to be clinical scepticism of genetic exceptionalism with regard to TPMT testing. This was summed up by consultant haematologist 2: *“People worry about all genetic testing but quite frankly we need to know that result... I don’t think that having a low TPMT level will affect anyone’s insurability or affect their mortgage or anything like that”*.

This view reflects the situation more broadly in the UK in that private health insurance is purchased only by a minority of people due to the broad coverage of the NHS, and a moratorium agreed between the Association of British Insurers and the Government on the use of genetic testing in insurance in almost all circumstances has been in place for several years and is likely to remain in place until at least 2011.⁷⁴

As the patients have little opportunity to discuss the test it is not clear to what extent they may understand the test or object to it on the basis of its possible ethical implications. One clinician’s response to this was that any objections would likely be very rare: *“You are not doing [the test] out of interest. There have been deaths in patients who have been deficient. It is a significant finding.”* (consultant haematologist 2).

If a physician did not use the TPMT test when it was available and their patient subsequently suffered an adverse drug reaction, the issue of culpability was considered to be a valid one because *“in oncology if you don’t follow [the protocol] the patient dies.”* (consultant haematologist 1). The clinical trial parent information sheet also clearly states that negligence could be grounds for legal action.⁷⁵ However there was no mention of this having arisen in the context of the ALL clinical trials.

Further information:

⁷⁴http://www.dh.gov.uk/PublicationsAndStatistics/PressReleases/PressReleasesNotices/fs/en?CONTENT_ID=4106051&chk=2CNwmM accessed 01/04/05

⁷⁵ See http://www.ctsu.ox.ac.uk/projects/ukall2003/UKALL2003v3_parent_info.doc accessed 01/03/05

TPMT testing is available in an NHS lab, beyond its use for ALL (which is undertaken in a research lab). The NHS lab provides a service for clinicians from a range of disciplines including Gastroenterology, Dermatology and Rheumatology where Azathioprine in particular is a commonly used thiopurine drug. It has been estimated that 60,000 patients commence Azathioprine each year in the NHS, and that TPMT testing in this area could benefit many of these individuals (lab3). The 3 UK laboratories undertaking testing at present, process perhaps 15,000-20,000 tests per year between them.

From the above case study we can see that TPMT testing does not offer a complete solution to ADRs related to thiopurine drugs. Furthermore it must be used in addition to existing procedures rather than replacing them. If TPMT is to be held up as a model example of PGx testing in practice, then it seems PGx cannot be said to represent a radical new paradigm. Rather it offers another tool for the medical armamentarium.

Interviews

3 laboratories, including multiple staff per laboratory.
2 pharmacists from different sites
3 senior consultant haematologists from 3 different sites
1 employee of the drug manufacturer
1 employee of a charity
1 employee of a private health insurer
+ personal communications with pharmacists, civil servants and physicians.

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5. Key findings of costs benefit analyses and case studies on TPMT and HER2 testing

In this chapter the key results of the cost-effectiveness studies and the descriptive studies of the Her-2 en TPMT tests will be described. Policy recommendations are beyond the scope of this report and only conclusions stemming from the data in the previous chapters are made. In 5.1 the main conclusions regarding the cost effectiveness analyses of Her2 and TPMT testing will be presented. In section 5.2 by the key findings stemming from the HER-2 testing case studies are presented in section 5.3 by the main findings of the TPMT testing case studies are presented.

5.1 Conclusions cost-effectiveness analyses

- **Cost-effectiveness analyses of applications of pharmacogenomics are sparse**

Although an increasing number of applications of pharmacogenomics are described in literature, the economic implications of pharmacogenomics are less often studied. In a recent systematic review of cost-effectiveness analyses of pharmacogenomic interventions Phillips and Van Bebber (2004) identified only 11 studies that met the inclusion criteria for a cost-effectiveness analysis.

- **Clarifying the economic implications of pharmacogenomic treatment strategies is important, as this may facilitate the implementation of pharmacogenomic treatment strategies**

Pharmacogenomic treatment strategies offer the potential to improve drug effectiveness, reduce adverse drug reactions and provide cost-effective care. However, pharmacogenomics has had little impact on clinical practice. Given the case studies we have conducted, the biggest barrier seems to be diffusion, with doctors not seeing the relevance of PGx for their practice. In addition, the newness of the technology is a barrier at the moment for using the tests; the tests are difficult to use and not always seen to provide added value. Information on cost and effectiveness of pharmacogenomic treatment strategies provided by cost-effectiveness analyses may partially reduce these barriers.

- **Scarce data available for studying the cost-effectiveness of TPMT testing (safety of thiopurine drugs) in children with acute lymphoblastic leukaemia**

Little information on the parameters for the TPMT model was specifically available for children with ALL. Therefore, estimates from pharmaco-economic studies on other thiopurine drugs are frequently used in this study.

- **Large differences in costs reported between countries**

The cost estimates reported by the participating countries in the project vary considerably. This may partly represent real differences in costs between countries, but also cost components included and estimation methods may differ.

For example the reported costs of the IHC test, for example, ranged from EUR 30 (the Netherlands) to EUR 190 (Ireland). The costs reported by the United Kingdom (EUR

130) and Germany (EUR 127-167) are in between. The Dutch estimate covered only material costs, while the other reported amounts include both material and personnel costs.

- **TPMT test has a favourable cost-effectiveness ratio**

The costs of TPMT screening are estimated to be EUR 141 per child with ALL. The costs per life year saved are assessed at EUR 2,102 per life-year saved. When discounted at 3%, the costs per life-year saved are EUR 4,760 per life-year saved.

- **FISH alone or FISH as confirmative test after an IHC positive result are preferable strategies for HER 2 testing**

A number of combinations of the IHC test and FISH test were studied in order to identify the most cost-effective test-treatment strategy. Using the FISH test as confirmation of all positive IHC results or using the FISH test alone are efficient strategies. This is in accordance with earlier studies.

5.2 Conclusions in HER2 testing

- **Role of industry in introduction of test differs between countries**

While in the UK and Germany industry, i.e. Roche had a very active role in the introduction of HER2 testing, in the Netherlands and Ireland other actors such as clinicians and patients were the driving forces. To put it in another way: in large markets industry is active in pushing the technology, in smaller markets this is left to the users: patients and doctors. The cost-driven scepticism about the HER2 testing that was apparent in all four countries was overcome by Roche in the UK through funding of all HER2 testing in the UK for a certain period of time and by making Herceptin available to clinicians. In Germany Roche approached specific pathological labs and persuaded them to become reference centres. This made doctors already familiar with the test and the Herceptin product. Roche also followed a massive marketing campaign. In the Netherlands Roche was not that active. It even doesn't sponsor a Dutch pathological lab that together with a German lab (which is sponsored by Roche) is performing a project for the implementation of the FISH test in their labs. In the Netherlands a relatively large amount of so-called home-brewed tests (developed by labs themselves and much cheaper) are on the market.

- **Practice of testing differs between countries**

In Germany, Ireland and the Netherlands and immunohistochemical HER2 testing is in most hospitals an integral part of a set of laboratory tests of breast tumour tissues. The outcome of the tests, together with other data (such as size of the tumour and positions of the tumour) forms the basis for an informed decision on the therapy to be used. The test can also be used as a means to forecast the probable development of the cancer. In the UK only 35% of the cancer centres routinely test for HER2 status on breast cancer diagnosis. However, Herceptin is not widely used, for several reasons, and also the protocols differ. In Ireland, Herceptin is not widely used (only in Stage IV metastasis). In Germany Herceptin is applied as a mono therapy as in combination with chemotherapy.

In the Netherlands Herceptin is used as adjuvant therapy (after a mama amputation) and when metastasis has been found (in that case in combination with chemotherapy). In the UK, Roche is still supplying (to some hospitals) Herceptin.

- **Quality schemes control quality of test**

The use of approved and labelled test kits, such as the one from DAKOCytomation is not enforced in any of the countries studied. Due to the high costs of these commercial kits, so-called home brewed kits have been developed and are used, mostly in-house. It is the QA scheme that 'regulates' the use of PGx tests in the four countries. Accreditation systems are in place (in most cases on a voluntary basis) in commercial labs; in most hospitals labs this is not the case. It is widely recognised that the more experience with the test, the better guarantee of the quality. Therefore, the number of tests conducted is considered as a reliable quality indicator. According to Roche 150 tests a year is a minimum. In the UK guidelines have been introduced that require an annual caseload of at least 250 cases. Irish labs that undertake her-2 testing participate in the UK QA scheme. The Netherlands also operates a system where colleagues assess each others' tests and develop quality standards.

- **Approval controversial in UK**

In Germany and the Netherlands approval of Herceptin and HER2 tests on the market followed the standard procedures and did not cause any specific difficulties. The appraisal of Herceptin in the UK was one of the most controversial decisions taken by the national authority in place (NICE). This was due to its nature as anti-cancer drug which meant that Randomised Clinical Trail (RCT) data for monotherapy had to be available. This gave delays and problems because it is deemed unethical to run a control/placebo arm in the treatment of metastatic breast cancer, where, by definition, it is clear that current treatment are ineffective.

In all countries both Herceptin and HER2 are covered by reimbursement procedures. However in clinical practice it was mentioned in three case studies that doctors deliberately do not mention the existence of the test because of the costs of the drug. By restricting provision of HER2 testing or, health authorities keep Herceptin prescriptions costs low. In the Netherlands treatment can be limited as the hospitals budget has reached its maximum. According to German law Herceptin should be reimbursed completely. However, due to limited hospital budget treatment of Herceptin is not reimbursed if the patient does not fit exactly the indicated score. In these case doctors do not inform their patients about the treatment. However, many patients are willing to raise own money to have access to a drug that might help them.

- **Patients push for use of test**

Patients' organisations have had an active role in the introduction of Herceptin and continue to push as still doctors do not fully inform patients about all treatment possibilities. In the four countries breast cancer patients are informed that a number of tests will be run on the tumour tissue, but HER2 testing is not specifically addressed before the results become available. However, breast cancer patients increasingly are informing themselves through the internet and patients organisations and ask the doctor about the test.

5.3 Conclusions on TPMT testing

- **Practice of testing differs between countries**

TPMT testing in children with ALL is not obligatory in the different countries and, as a result the frequency of TPMT testing differs between the four countries. In the Netherlands testing is only conducted when deficiency is expected, in Germany this is also the case. In the UK and Ireland, almost all children are tested, but this is within a research project. It is not clear whether this will be the case when the research is finished in 2007.

- **The main barriers of testing in all countries is: lack of knowledge of physicians, not perceived utility by physicians, (lack of usefulness) and lack of (industrial) push.**

There is little formal training or guidance for doctors and other medical staff in how to interpret PGx test results and only informal mechanisms to ensure they understand the interpretation sufficiently. As such staff are often dependent on laboratories to supply information on how to interpret the results. However, this is not only the case for TPMT testing, but for pharmacogenetic testing in general.

It appeared that physicians frequently do not feel the urgency for testing patients on TPMT deficiency before starting therapy. One reason was the rare frequency of occurrence of adverse reactions in many cases. The number of tragic or even lethal incidences can in time be prevented by regular monitoring of the patient. In addition, the PGx test can not substitute regular thrombocyte monitoring, because TPMT polymorphisms can only partially explain occurring pancytopenia and leukopenia, especially if they occur after more than four months after the commencement of the therapy. This leads to additional workload instead of less work for the physicians and additional costs.

The diffusion of the test is not strongly promoted by a pharmaceutical company or by another organisation, such as a patient group. This is probably due to the small economic size of market. Although market size could be increased by using TPMT tests in other diseases where thiopurine drugs are used, such as rheumatoid arthritis, it is not expected that drug firms are interested in promoting PGx test use.

Ensuring diffusion of tests is not specific for pharmacogenetic tests. In general, technological diffusion takes a long time.

- **Until now, no societal issues**

Until now, no problems are perceived by physicians in asking for informed consent for a TPMT test. In addition, parents said not to be concerned with genetic testing when cancer is the issue. However, with increasing patient knowledge, physicians might be sued for not testing children in case of severe toxicity. Until now, this has not happened.

- **TPMT testing can not easily generalized to other types of pharmacogenetic testing**

TPMT testing in children with ALL seems to have a low priority to physicians. However, this is likely because of the specific nature of the disease and treatment. In this disease TPMT testing does not offer a complete solution to adverse reactions related to 6-MP. In addition, it must be used in addition to existing procedures rather than replacing them. However, the perceived utility of TPMT testing might be different in other patient groups, such as rheumatoid arthritis. Therefore, TPMT testing in children with ALL can only partially be seen as a model example of pharmacogenomic testing in practice. More research is needed.

5.4 Conclusions

The findings reported here are specific to the case studies of TPMT and Her-2. It is not clear to what extent these findings may be generalisable to other PGx tests. However the following conclusions are put forward:

- The pharmaceutical industry's interest in PGx seems limited to large markets: they have pushed HER2 and Herceptin in Germany and the UK, but were rather passive on the Dutch and Irish markets. They have not expressed interest in PGx for TPMT.
- The introduction of a PGx test requires education of a wide range of medical staff; they have to learn to use and interpret the tests correctly. This is a barrier for the introduction of the tests. QA schemes and undertaking a high volume of tests each year are readily available options to ensure higher quality of laboratory testing.
- Due to the high cost of commercial tests, hospitals laboratories have developed their own so-called home brewed tests. Producers of commercial test kits, as well as some laboratory staff raise questions concerning the quality of some of these home brews (see also Part 3 of this study).
- PGx may be an addition to the medical armamentarium but is not necessarily going to replace existing practices. As has been shown in the TPMT case study, TPMT testing does not offer a complete solution to adverse reactions related to thiopurine drugs. It must be used in addition to existing procedures rather than replacing them.