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Institute for Prospective Technological Studies (Seville)
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Polymorphic sequence variants in medicine: Technical, social, legal and ethical issues Pharmacogenetics as an example

ESHG/IPTS Background document (Draft)

Index

1 Introduction

Traditional genetic services have focused on single gene disorders, chromosomal abnormalities, malformation and mental retardation syndromes and infertility problems, including the provision of laboratory investigations. Major progress has been made in elucidating the genetic basis of monogenic (single-gene) disorders, such as cystic fibrosis, Huntington disease and Duchenne muscular dystrophy and in applying this knowledge in clinical practice. Much of this work pertains to obstetric and pediatric practice and to the management of individually rare but collectively significant groups of genetic disorders.

Now, another major challenge to genetic medicine is posed by so-called 'complex' conditions, which include common diseases such as diabetes, heart disease, cancer, and psychiatric illness, as well as variable responses to treatment, including lack of efficacy or susceptibility to adverse drug responses.

When compared to classical monogenic disorders, this category of conditions is generally characterized by (i) a substantially higher population frequency and, therefore, a higher public health impact - requiring the movement of genetics from a medical specialty into the clinical mainstream, (ii) the involvement of variants at multiple genes, most probably interacting with one another, (iii) the presence of relatively minor effects exerted by individual variants ("susceptibility factors"), and (iv) a much more important role of environmental triggers. Taken together, these differences imply that the challenges in finding and analyzing the role of genes responsible for complex conditions represent a quantum leap from those encountered with single-gene disorders.

Currently, an improved understanding of genetic susceptibility to adverse and variable drug response (i.e. "pharmacogenetics"; please refer to a more complete definition in section 3.2) seems as though it could offer more immediate clinical returns, since some drug response traits can be simpler than those of complex disease. There are some examples of monogenic effects on drug response, (Goldstein *et al.* 2003) such as thiopurine methyl transferase which will be discussed in section 6.3 of this document. Also, some pharmacogenetics research is entwined in the genetics of complex disease; i.e. by identifying associations between genetic markers for drug response and those genes involved in the inherent susceptibility to the disease itself. In this way, diseases may perhaps be reclassified on the basis of a 'molecular taxonomy,' and patients (and therefore their medications) may in the future be stratified (Hedgecoe and Martin 2003).

A multitude of journal articles have predicted the widespread use of pharmacogenetics in the near future. Some of them predicted this use would be happening already, and others suggest that as a new technology, it will take time for the applications to evolve into clinical practice. The use of pharmacogenetics has not yet come into common clinical practice in primary health care clinics; however, there is currently insufficient solid evidence to be either overly optimistic or skeptical that this will come to fruition (Sevilla 2004).

This document is intended to give an overview on the topic of polymorphic sequence variants in medicine, by delving into issues regarding pharmacogenetics as an example of this topic. Though this subject is not one that exemplifies all aspects of polymorphic sequence variants in medicine, it is one that is currently active in public discourse, and for that reason was investigated further by us at this time.

2 Methodology

To construct this background document, we reviewed existing literature that was identified by using PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) and a whole host of keywords including 'pharmacogenetics', 'pharmacogenomics', and 'complex disease,' in combination with all of the subheadings utilized in this document. Additional articles were found by mining the bibliographies of this literature.

Information for appendices I and III was found by searching the websites of European Agency for the Evaluation of Medicinal Products (http://www.emea.eu.int), and EUROPA (http://europa.eu.int). Appendix II was adapted from a previous PPPC document on the provision of genetic services in Europe. All three appendices were then updated by members of the PPPC and the organizing committee of a workshop on pharmacogenetics.

Comments received from European experts on a first draft, as well as the ideas expressed at a March 2004 workshop, have culminated in this final draft of the document. ESHG will also draft recommendations on this topic which will be placed on the ESHG website (www.eshg.org) for public consultation and discussion.

3 Terminology

3.1 Genetic variation and polymorphic sequence variants

A majority of the genetic variation between human beings is attributed to single nucleotide polymorphisms (SNPs). These SNPs are locations in the genome where single bases are found to differ between individuals; for instance in a particular location of the genome, person 1 has a guanine, and person 2 has an adenine. There is not a consensus as to the precise differentiation between polymorphisms and mutations. Though, the label of polymorphism is often applied to sites in which the rarer base occurs within the population at a frequency of greater than 1%; whereas, germ-line variations of less than 1% are typically referred to as mutations (Kirk *et al.* 2002).

3.2 Pharmacogenetics and Pharmacogenomics

Pharmacogenetics and pharmacogenomics are mostly used interchangeably in the literature to mean the study of individual variation on drug response. Though the word pharmacogenetics has been in circulation for several decades (it was used by Vogel in 1959), pharmacogenomics is a new term - first published in 1997 (Hedgecoe 2003). Some make a distinction between the two words, stating that pharmacogenetics is more specifically the impact of the variation of a single gene on drug response, and that pharmacogenomics encompasses a broader scope, to include the impact of interactions within several genes on drug response (Moldrup 2001, Anderson *et al.* 2003), and relating to industry goals of "identifying candidate genes and polymorphisms, correlating these polymorphisms with possible therapies, predicting drug response and clinical outcomes, reducing adverse events and selection, and selecting dosing of therapeutic drugs on the basis of genotype" (p300 Issa 2002). Many still believe that pharmacogenetics is a term that can encompass both definitions; for an interesting review regarding hypotheses on why pharmacogenomics came to be as a term, please refer to Hedgecoe 2003.

Definitions for these terms have been proposed by the United States Food and Drug Administration. In their Draft Guidance for Industry: Pharmacogenomic Data Submissions released on November 3, 2003, they use pharmacogenomics as a general term to describe "the use of a pharmacogenomic or pharmacogenetic test... in conjunction with drug therapy (p1 FDA 2003)." They later define pharmacogenetic test as "an assay intended to study interindividual variations in DNA sequence related to drug absorption and disposition (pharmacokinetics) or drug action (pharmacodynamics) including polymorphic variation in the genes that encode the functions of transporters, metabolizing enzymes, receptors and other proteins;" and a pharmacogenomic test as "an assay intended to study interindividual variations in whole-genome or candidate gene single-nucleotide polymorphism (SNP) maps, haplotype markers, and alterations in gene expression or inactivation that may be correlated with pharmacological function and therapeutic response (p15 FDA 2003)."

The European Agency for the Evaluation of Medicinal Products (EMEA) published a position paper in 2002 on terminology in pharmacogenetics, as they felt that by forming accepted definitions of the two words, they would be more easily applied within clinical trials. They defined pharmacogenetics as, "the study of interindividual variations in DNA sequence related to drug response (p3)" and pharmacogenomics as "the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The term is broadly applicable to drug design, discovery, and clinical development (p3)." For the purposes of this paper, we will utilize the EMEA definition.

4 Current state of research

4.1 Identification of polymorphic sequence variants

It is estimated that approximately 10 million sites in the genome could be designated as SNPs, which comprise 90% of human variation (International HapMap Consortium 2003). The SNPs that are thought to most likely contribute to complex disease are those in the coding sequences that alter the gene protein products. However, most SNPs are located in non-coding regions of the genome, which have no known impact on phenotype. Nevertheless, these SNPs, particularly those in regulatory regions, may also contribute to susceptibility for common complex diseases (Syvanen 2001). Over 3 million non-redundant SNPs were listed in public repositories as of February 2003, and as of December 2003, public databases contained over 5 million human SNPs (International HapMap Consortium 2003, Marnellos 2003, Ulrich *et al.* 2003). This number is predicted to increase as research efforts continue. SNPs are stable markers, and as they are quite numerous and distributed across the genome, they are thought of as excellent landmarks to guide the discovery of genes that are involved in health and disease (Marnellos 2003). Comprehensive reviews of SNP genotyping technology can be found in: Kwok and Chen 2003, Kirk et al. 2002, & Syvanen 2001.

Research is currently underway using SNPs to discover susceptibility genes for complex disease and factors involved in drug response. Though there are some companies constructing systems for SNP genotyping, it is felt that large-scale genotyping assays are currently not feasible for routine clinical practice. For this to happen in the near future, as there is hope that soon it will, costs (including special instrumentation and reagents) need to be affordable, and reactions must be able to be performed in large quantities to meet the demand (Kwok and Chen 2003). As activities such as the Human Genome Project and The SNP Consortium (http://snp.cshl.org/) progressed, so did the impetus to streamline techniques for SNP discovery. Now they are more automated, less expensive, and more efficient than they were 10 years ago, and are continually being refined. Current technologies for analyzing SNPs fall into two basic categories: hybridization or enzymatic. Each technique has its own advantages and disadvantages in throughput, sensitivity, and specificity; however no technique is perfect for all applications, so new approaches are still being sought for the future of SNP genotyping (Kirk et al. 2002, Kwok and Chen 2003, Marnellos 2003).

4.2 Research strategy

Study design of pharmacogenetic research can use knowledge gained from clinical research/clinical trials, as well as genetic epidemiology of complex disease (Sevilla 2004). The traditional methods of monogenic disease gene identification, including family-based studies and linkage analysis, are much more challenging when dealing with complex common diseases such as heart disease, psychiatric disorders, and diabetes (Marnellos 2003), as well as for the genetic susceptibility to adverse drug response or variable response. Also, there is a shift in focus when doing pharmacogenetic research since one generally is not looking for the heritability of a drug response, and is instead investigating variants that predict or explain drug response; in the second case, many academic researchers feel that association studies are more appropriate (Sevilla 2004). Family based association studies are relevant for highly penetrant traits as well – as they are still association studies – and the other family members would not have to necessarily take the drug in question. For pharmacogenetic association studies, it is important to have a suitable sample size, good controls, a well-defined phenotype, a model to investigate interactions, and study replications. Prospective studies are important to determine if a pharmacogenetic test improves outcome; however, this is almost never done in pharmacogenetic research (Sevilla 2004).

There are two primary strategies for making genotype-phenotype correlations. First is the genome-wide association approach, with no *a priori* hypotheses as to which genes are involved with the trait. The second approach is to screen a selected set of 'candidate genes' deemed potentially relevant to a pharmacological response for variation in DNA sequence - either specific to a particular drug, or to a particular disease (Hoehe *et al.* 2003, Schneider *et al.* 2003, Sevilla 2004).

4.2.1 Genome wide association study

The abundant sequence diversity uncovered in humans is much greater than initially expected (Chakravarti 1998), necessitating researchers to seek tools in which to represent this variation. One method is to use linkage disequilibrium (LD) to select genetic markers that are associated with many other variants in the genome (Goldstein *et al.* 2003). The pattern of LD within genes is more complicated than previously estimated, and the LD can differ between populations, thus adding to the complexity (Sevilla 2004). Stephens *et al.* have shown that the possibility of any particular pair of SNPs of being in LD is not predictable and, as a result, LD should be determined empirically for any specific genomic region (Stephens *et al.* 2001). Sets of SNPs were found to exist in blocks of strong LD, indicating a haplotype block structure of the human genome. Haplotypes are now considered as useful tools to use when looking for associations between phenotypes and genomic variation (Daly *et al.* 2001, Stephens *et al.* 2001), since single SNP-based candidate genes studies may be statistically weak; true associations may be missed and negative results exclude a particular SNP though not necessarily the gene (Hoehe 2003).

This rationale provides the basis for the development of the HapMap. An international consortium has recently been formed to determine the common patterns of genetic variation (haplotype blocks), and by genotyping a projected 1 million SNPs in populations from around the world, they plan to make freely available to the public the SNPs that will most effectively represent human genetic variation (International HapMap Consortium 2003). For a comprehensive review on LD and haplotype blocks, please refer to: Wall and Pritchard 2003.

Are haplotypes a reliable tool? Schwartz *et al.* investigated the validity of the haplotype block concept and found that indeed different block decompositions of a single genetic region tend to be far more consistent than can be explained by chance, though absolute similarity is frequently small. It therefore appears that while there is a common underlying structure to haplotype blocks that all methods detect, that structure is less rigidly defined. In conclusion, it is thought that haplotype blocks are valid but require greater sample sizes or better algorithms for reliable detection (Schwartz *et al.* 2003).

Efforts are being made to enumerate the full array of genetic variation in all genes, establish their haplotypes and employ the so-called "haplotype tags" SNPs (htSNP) to capture the information in a gene. This gene-based haplotype marker represents underlying LD and haplotype structures of the genes (Johnson *et al.* 2001). Current approaches to distinguish haplotypic variation in a population rely on statistical analysis of transmissions rates (Sebastiani *et al.* 2003). One question is if htSNPs can represent all genetic information. It seems it can for most alleles with frequencies greater than 5-6%; however, for those below this threshold, a direct approach is needed (Sevilla 2004).

Also, it has been stated that there is currently no proof of concept for using genome wide profiles (i.e. anonymous markers) to predict drug response, and some feel that there are reasons to be skeptical about this in the near term. It is difficult to develop a test that has appropriate predictive value when focused on specific causal polymorphisms; however, when using genome wide markers that are in linkage disequilibrium with the causal variants, then the patterns of association may vary between populations, therefore changing the predictive value of the test to at least some degree. It is likely to be some time before these are used clinically. For this reason, pharmacogenetic tests seem for some researchers to more likely begin with specific causal polymorphisms (Sevilla 2004).

Sometimes haplotypes are ineffective. An under-explored area of research is that of high-risk variants that are relatively rare (<1%); in these situations, the variants will most likely not be available in SNP banks and not tagged by common haplotypes. Functional haplotypes can be more revealing, and appropriate selection of phenotype is essential to identify strong effects. Polymorphisms often exert their effects through complex systems in which buffering, feedback, redundancy, and robustness exist, therefore diluting their effects. Due to this, relating single polymorphisms to a multifactorial trait could possibly reveal only a small fraction of the genetic contribution; biological *systems/pathways* are therefore suggested by some as a more appropriate unit to investigate for a complex trait (Sevilla 2004).

4.2.2 Candidate gene approach

One pharmacogenetics approach is to investigate polymorphisms in candidate genes (Mohrenweiser 2003). The systematic analysis of candidate genes has neither been feasible nor practicable until the late 1990's, even though the sequences of significant candidate genes had been available since the 1980's (Hoehe *et al.* 2003). Only in the late 1990's has increasingly systematic DNA sequencing allowed candidate gene analyses to gain more quality. These candidate genes include drug targets and genes involved in disease, metabolism, absorption, excretion or transport. The "gene-based functional" haplotype becomes then the most relevant (Hoehe 2003). Hoehe sees a major future challenge in the increasing multiplicity of haplotypes and the identification of their relation to function and phenotype (Hoehe 2003). She proposes classification by sequence-structure-function of haplotypes as a way to reduce complexity "that will be critical for the evaluation and prioritization of drug targets, for the valid stratification of population subject to pharmaceutical intervention and for the elucidation of the molecular causes of individually different drug response" (p561 Hoehe 2003). Other future key challenges:

- Need to systematically and comparatively sequence entire individual genomes and genes as soon as technology allows
- Functional analysis will have to change from classical *in vitro* single mutation analysis to the functional analysis of entire individual gene sequences.
- Elucidation of the biological significance of the haplotype structure.
- Resolve controversial definition of "haplotype block structure" and develop techniques to validate them *in silico*, *in vitro* and *in vivo*.

The low predictive value of pharmacogenetic tests for most polymorphic variants reduces the clinical utility of the tests. (For detailed reasons, please refer to Holtzman 2003).

Also, the current pharmacogenetic research is seemingly not ideal, as it does not produce adequate data of high quality for estimating effects. Reasons for this include small sample sizes, genes studied independently (i.e. few studies investigate interactions), and population stratification is often ignored (Goldstein *et al.* 2003, Sevilla 2004). Once a variant is seen to have an effect, it is still very difficult to transpose it clinically as gene control is quite complex. Association also does not always equate to clinical utility since predictive values must be determined accurately, and both environmental and genetic interactions are likely (Sevilla 2004).

4.3 Methodological issues

4.3.1 Interpreting genetic variation

It is suspected that susceptibilities to common complex disease and variable drug response involve an interplay of polymorphisms in several interacting genes, as well as an environmental component, and gene/environmental interactions. Adding to this complexity, it is possible that certain polymorphisms confer susceptibility when in certain gene/environment backgrounds, but not in all contexts (Kirk *et al.* 2002). Due to this, a high degree of susceptibility cannot necessarily be deduced from a single locus. Furthermore, variations found within suspected genes are most likely not necessary or sufficient to cause the phenotype in question (Altshuler *et al*. 2000).

4.3.2 Statistical power of studies, and multiple testing issues

Power analyses compute the probability to see (or miss) an effect present. Genetic models have more parameters for this than the average clinical trial. One can calculate power *given* a special situation modeled; however, a general situation has many underlying parameters, thus making problematic the assessment of the power of most studies (Sevilla 2004).

Depending on the study design, as many as 5,000 tests may be needed to evaluate strong functional candidates; a low false-positive rate would be provided by a *P* value of 10^{-5} (0.05/5000). When undertaking a genome-scan, without having evidence of any functional candidates, 250,000 – 500,000 tests may need to be performed; for a low false-positive rate in this instance, the *P* value should be 10^{-7} to 10^{-8} (Buckland 2001, Dahlman *et al.* 2002).

Due to the nature of association studies, multiple tests are performed on the same patient samples, which have to later be statistically corrected for since a high false-positive rate would result. How to correct for this is still under debate. The Bonferroni correction (which was used in the previous paragraph) could overcorrect for the inflated false-positive rate, and as a consequence, valid information would be discarded; however, under-correction would result in the existence of false-positives. A thorough analysis of this (Lohmueller *et al.* 2003) has shown that there is publication bias, but it cannot explain all positive associations. Unfortunately, it seems the publication bias towards positive results has propagated publication of studies with a high potential for false-positives. What is even more concerning than the incidence of false-positives is the potential lack of detecting genuine effects (Cardon and Bell 2001).

Some have posited that bioinformatics may be able to contribute in this realm by compiling multiple association studies results. However, the difficulty in combining all information ever gathered is that there are currently no definitive standards in place. Therefore, putting all disparate data together would most likely not be a helpful endeavor (Sevilla 2004).

4.3.3 Relevance for the different populations

Globally distributed gene-based sequence variations are at a frequency of at least 2% and population-specific variants are at least 5% (Stephens *et al.* 2001). Nearly 80% of all haplotypes occur in all populations while only 8% are population-specific (Stephens *et al.* 2001).

Research has investigated SNP maps within different populations (Japanese and European). It was found that one needs 20% more SNPs to be able to cover both populations, versus just one. This has not yet been investigated for African populations, but is expected to increase since the LD is greater (Sevilla 2004).

For additional information on this topic, please refer to the section 10.3 entitled: "Genetic variants associated with ethnic groups."

5 Current activities in the research area

5.1 Examples in complex disease

Genome scans for susceptibility for common diseases have increased in number in recent years, thanks to the increase in SNPs discovered, and the increase in technologies used to scan for them. The types of studies are quite varied: from large-scale association studies, such as looking for polymorphisms that may contribute to morbidity (Kammerer *et al.* 2003), to searching for myocardial infarction susceptibility (Ozaki *et al.* 2002), to linkage-study genome screens for genetic factors of Parkinson's disease (Scott *et al.* 2001); to as specific as scanning previously found susceptibility loci to hunt for the genes in which polymorphisms/mutations may confer disease susceptibility.

Scans within known susceptibility loci have been performed for a wide scope of diseases/phenotypes. Some examples from the past few years include: risk of ischemic stroke (Gretarsdottir *et al.* 2003), associations with typical migraine (McCarthy *et al.* 2001), psoriasis susceptibility (Hewett *et al.* 2002), rheumatoid arthritis susceptibility (Okamoto *et al.* 2003), Crohn's disease susceptibility (Hugot *et al.* 2001, Rioux *et al.* 2001), type-2 diabetes mellitus associations (Horikawa *et al.* 2000), and susceptibility to autoimmune disease (Ueda *et al.* 2003).

Research is also being performed on investigating SNP haplotypes within known (or suspected) genes associated with disease such as the *RET* and Hirschsprung disease (Griseri *et al.* 2002, Borrego *et al.* 2003), *APOE* and Alzheimer disease (Martin *et al.* 2000), Tau gene and late-onset Parkinson's disease (Martin *et al.* 2001), and *BDNF* and obsessive-compulsive disorder (Hall *et al.* 2003).

5.2 Examples in pharmacogenetics

According to recent research, approximately 500 human gene products are targeted by today's medicines, and it is predicted that 5,000-10,000 genes and gene products could be important targets and/or therapeutic proteins (Kurth 2003, Parazzolli and Recchia 2004). Pharmacogenomics could provide new targets from the study of genes involved in the disease. The hard questions are, how to select these targets, and then how to validate them? Disease-related susceptibility genes are studied, as well as researching genes that belong to similar families (based on their sequence homologies). Functional genomic technologies are then employed to work further towards validation (Roses 2000). A substantial portion of the person-to-person variability in drug response is believed to also be genetic in nature. Variations in genes for drug-metabolizing enzymes, drug receptors, and drug transporters have been associated with individual efficacy of medicines and the occurrence of adverse drug reactions (Pirmohamed and Park 2001, Johnson and Lima 2003).

5.2.1 Cytochrome P450

The best-known example is the variation in the drug metabolizing enzymes of the cytochrome P450 (CYP) family – such as the debrisoquine/sparteine type, which was first mapped in 1987 (Eichelbaum *et al.* 1987). In the CYP2D6 gene alone, there are more than 70 allelic variants that have been detected (www.imm.ki.se/CYPalleles/cyp2d6.htm). These alleles are responsible for variation in enzyme activity resulting in high or low activity and even ultra-rapid metabolization of a drug. Poor metabolizers are more likely to have adverse drug effects than extensive metabolizers, as the drug could have a higher chance of accumulating to toxic levels in an individual's system.

5.2.2 Oncology

In addition to evaluating one gene in isolation, pharmacogenomic research of interest in oncology includes targeted investigation of pathways involved in treatment response, to then have a composite view as a tool to modify individual therapy. This includes the folate metabolism pathway, and the interaction of genes such as 5,10-methylenetetrahydrofolate reductase (MTHFR), reduced folate carrier (RFC), and thymidylate-synthase promoter-enhancer (TSER), with chemotherapeutic agents such as methotrexate and 5-fluorouracil (Ulrich et al. 2003). Other studies are investigating the effects on 5-fluroruracil therapy by gene expression levels of the thymidylate synthase gene (TS), the thymidylate phosphorylase gene (TP), and the dihydropyrimidine dehydrogenase gene (DPD); as well as the effects on therapy of platinum agents such as cisplatin and oxaliplatin by polymorphisms in excision repair cross-complementation group 1 (ERCC1), glutathione S-transferase P1-1 (GSTP1-1), and DNA repair gene XPD (Lenz 2003). Also, clinical responsiveness to the tyrosine kinase inhibitor gefinitib in patients with non-small-cell lung cancer has been predicted through screening of the human epidermal growth factor receptor (EGFR) for specific mutations (Lynch *et al.* 2004).

Though drug-related toxicity almost always depends on the genotype of non-tumor tissue, it is important to note that polymorphisms in both the individual's genome, as well as tumor genome, can affect drug response (Ulrich *et al.* 2003).

5.2.3 Psychiatry

Research is currently being performed in the field of psychiatry, regarding the effects of metabolic polymorphisms as well as the influence of neurotransmitter receptors and transporter proteins (Staddon *et al.* 2002). Well documented are the effects of CYP2D6 and CYP2C19 polymorphisms on the pharmacokinetics of a wide-variety of anti-depressants. Due to this, recommendations have been published on dosage levels for antidepressants based on CYP2D6 and CYP2C19 genotyping (Kirchheiner *et al.* 2001). The data on which these recommendations have been based came from Caucasian populations, so it is suggested that their recommendations may not be applicable to other populations such as African or Asian. It also underscored that dosage should continue to be individually determined, taking into account other traditional factors including: age, sex, severity of depression, liver disease, and any other medications the individual is currently taking. Their rationale for these recommendations is that "the existence of many other partially unidentified variables resulting in inter-individual differences in drug response should not detract us from considering known determinants" (p187 Kirchheiner *et al.* 2001). There has been a recent publication contradicting these recommendations, by

stating that CYP2D6 polymorphisms are "probably not of relevance to antidepressant side effects and therapy" and point to their studies with the medications fluoxetine and nortriptyline as examples (Roberts *et al.* 2004).

5.2.4 Cardiology

Cardiology is another field that has noted that medications for their patients are not efficacious for all individuals, and can have adverse side effects. Once reliable genetic testing is found, it has the potential to eliminate the trial-and-error approach of current prescribing practices (Humma and Terra 2002). However, this research is still in its infancy. Drugs in the following categories are currently being investigated for pharmacogenetic interactions: antiarrhythmics, drugs within the renin-angiotensin system, β-adrenoreceptor blocking drugs, diuretics, statins, anticoagulants, antithrombotic/antiplatelet agents, and digoxin (Humma and Terra 2002, Anderson *et al.* 2003). Variant alleles of the following genes of the cytochrome P450 enzymes have been implicated in the poor metabolizer phenotype associated with adverse reactions of cardiovascular disease drugs: *CYP2C9* with warfarin; and *CYP2D6* with metoprolol, carvedilol, propranolol, propafenone, mexiletine, and flecainide. However, across groups, the prevalence of these alleles varies greatly (Anderson *et al.* 2003).

Genetic variants of other proteins are also currently being investigated for their effects on cardiovascular drug efficacy, such as: N-acetyltransferases, UDP-glucuronosyltransferases, apolipoprotein E, angiotensin-converting enzyme, adrenergic receptors, and the P-glycoprotein (P-gp) transmembrane efflux pump (Anderson *et al.* 2003, Siest *et al.* 2003). Some researchers are taking such results to the next level, such as Gage *et al.* (2004) who developed an algorithm to include pharmacogenetic test results of CYP2C9 as well as clinical factors to predict an individual's maintenance dose of warfarin. However, a preponderance of the literature on this topic underscores that there still exists the challenge to get to sound clinical endpoints of pharmacogenetic testing to treat cardiovascular disease, due to multiple implied mechanisms, multifactorial complex traits, and weak effects of multiple genes interacting with environmental inputs; nevertheless, the overall tone is optimistic.

5.2.5 Other specialties

Pharmacogenetic research is also being performed in other arenas of medicine. Infectious disease applications of pharmacogenetics are still in the early stages of development. They currently include investigation into HLA alleles and antibody response to a vaccine, as well as IL-10 polymorphisms and interferon alfa treatment for chronic hepatitis C (Hayney 2002). Other investigations into HLA alleles include Mallal et al. (2002) and Hetherington et al. (2002) who found associations between HLA alleles and hypersensitivity to abacavir, an antiretroviral medication for HIV/AIDS. An association has also been found between an HLA-B allele and carbamazepine induced Stevens-Johnson syndrome (Chung et al. 2004).

The gastrointestinal realm is currently beginning to study pharmacogenetic applications to treatment for inflammatory bowel disease (IBD). Current efforts include investigating how the glucocorticoid receptor β influences corticosteroid response, and the metabolism pathway of 6-mercaptopurine/azathioprine, which includes thiopurine methyl transferase (TPMT) (Sartor 2003). Pharmacogenetic studies are also underway for the treatment of asthma (Pignatti 2004). Also, studies have suggested that a pharmacogenetic test could possibly highlight those with an increased susceptibility to teratogenic effects of medications such as valproate (Van Dyke *et al.* 2000, Duncan *et al.* 2001).

6 Clinical applications

6.1 Rationale for testing

6.1.1 Personalization

Though many articles state that pharmacogenetics is ushering in an overhaul of the medical system by making possible 'personalized' or 'individualized' medicines, this is not literally true. Instead, from a patient's point of view, pharmacogenetics is projected to help the physician/patient in the selection of certain available medicines, and the dosages for them; indeed not custom-manufacturing a drug for each and every patient. There may be some specialization, but that will be by stratifying patient populations into groups based on their genetic profiles,

and for each group there will hope to be a specialized medicine, and/or dosage. Also, factors other than a pharmacogenetic test can point a physician to a correct medicine (and dosage) for their patient, including diet, age, sex, smoking and alcohol intake, and liver function; how this will be integrated into the future of pharmacogenetics remains to be seen. It seems likely that pharmacogenetics will help with appropriate drug selection in the future, beyond the 'one size fits all' mentality that is in use today. However, by touting 'individualization' the public is being misled as this field cannot guarantee a perfect personalized prescription for everyone (Schmedders *et al.* 2003).

The standard of care that will result from the implementation of pharmacogenetics is more likely to be group standards versus individualized ones. For example, prescription of a certain drug may be restricted to those who are more likely to be a 'high-responder' given their genotype. However, though this makes sense from the perspective of the group, would it not seem rational for an individual to want access to a drug despite those results (especially if it is the only treatment option)? How will this be handled by regulators, health professionals and insurers (Buchanan *et al.* 2002)? It seems that this may be handled case by case, and indeed will affect only a few medicines (Sevilla 2004).

6.1.2 Stratification

With pharmacogenetics coming into practice, the stratification and segmentation of drugs and populations will increase. With this stratification, there will be medicines marketed towards particular (segmented) groups of the population. This stratification could be viewed in a patient or disease frame of reference. In referring to patient stratification, it would imply that the patient genotype would dictate differential dosing or targeting. In the frame of disease stratification, patients with like symptoms would be subdivided based on their genetic profile, and be prescribed different medicines (Shah 2003).

Current examples of stratification due to knowledge of genomic expression include the prescriptions of Herceptin (trastuzumab) and Gleevec (imatinib mesylate). The first is indicated for a subpopulation of breast cancer and pancreatic cancer patients with tumors that over-express the HER2 gene, and the second is for patients with Philadelphia chromosome positive chronic myeloid leukaemia, as well as for those with gastrointestinal stromal tumors with selective *c-kit* oncogene-activating mutations (Phillips *et al.* 2001, Shi *et al.* 2001, Ross and Ginsburg 2002, Goldstein *et al.* 2003).

6.2 Foreseen applications

6.2.1 Improving safety?

One reason why some individuals experience adverse drug reactions (ADRs), and others do not, is genetic variation. Some ADRs were previously considered to be unpreventable, as they were caused by inherent properties of the drugs themselves – however, pharmacogenetics may help change that, especially for medications with a narrow therapeutic window (Sevilla 2004). By genotyping an individual and noting if he/she was a poor/extensive metabolizer of a drug, one could either modify the dose accordingly, or prescribe a drug from a different metabolic pathway (Phillips *et al.* 2001). In this way, the use of pharmacogenetics could help an individual to avoid some, but most likely not all, side effects. It is reiterated that in many cases pharmacogenetics will not replace the necessity for careful clinical monitoring (van Aken *et al.* 2003), and some suggest that pharmacogenetic testing is itself just another form of monitoring (Sevilla 2004).

Phillips *et al.* performed a literature review on adverse drug reaction studies, as well as a review on variant alleles of drug-metabolizing enzymes. By comparing the two lists, they found that 59% of drugs in the ADR studies were metabolized by at least one enzyme known to have a 'poor metabolism' allele; this was in comparison to 22% of randomly selected drugs available in the United States. They concede that their study is not definitive, but state that it adds credence to the hypothesis that "genetic variability in drug metabolizing enzymes is likely to be an important contributor to the incidence of ADRs" (p2275 Phillips *et al.* 2001). They also listed 'Criteria to evaluate the potential impact of pharmacogenomics information in reducing adverse drug reactions' and 'A clinician's checklist for evaluating the potential role of pharmacogenomics in reducing adverse drug reactions' (see pp2276-2277 Phillips *et al.* 2001).

Adverse drug reactions result in high costs now, but it is uncertain at present as to what extent pharmacogenetics could decrease this, as a lot of this is due to prescription error, etc., and many adverse effects are never reported (Sevilla 2004).

However, Lindpaintner (2002) has highlighted some of the hurdles he believes are associated with utilising pharmacogenetics to improve safety, particularly adverse events of a serious nature. One is that there is a continuing high likelihood that even a small number of ADRs can result in withdrawal of a drug from the market. Secondly, that a small sample size may not provide enough data to show robust correlation with a particular genotype. Thirdly, that drug regulators may impose higher hurdles for associations related to serious adverse events in order to avoid administration of the drug to the 'wrong' patient. An exception to this rule would be for diseases that are life-threatening in their own right, where the potential toxic effects of ADRs would be outweighed by the dire prognosis if left untreated. For these reasons, Lindpainter has argued that overall, pharmacogenomics may have its greatest effect in terms of improving efficacy (Lindpaintner 2002).

6.2.2 Improving efficacy?

It is often mentioned that pharmacogenetics will improve efficacy by honing in on the 'right' drug and dose for an individual, given their genotype. It should be stated that this will not be the case for all medications in the future; however, pharmacogenetics will provide a possibility to identify patients who are less unlikely to respond to some medications, for example the HercepTest. As is the case with some pharmacogenetic tests, HercepTest investigates expression levels, and not the DNA itself. As previously mentioned, the medication Herceptin targets overexpressed HER2-receptors, so it will not be efficacious in patients that do not present this overexpression. Restricting prescription of Herceptin to those who have cells with such overexpression, leads to an overall improvement of the efficacy of this drug (Sevilla 2004).

6.2.3 Improving health?

From the previous two sections, it seems that pharmacogenetics, if and when it enters the clinical mainstream, could be used to improve patient therapy by helping decide how some drugs are selected and prescribed. However, it also needs to be reiterated that a majority of pharmacogenetic tests will likely be similar to other tools in medical practice, and yield probabilistic results rather than definitive predictions (Buchanan *et al.* 2002, Lindpaintner 2002).

For health care, the expected positive impacts are to reduce the overall cost of disease management for the individual through increased drug efficacy and safety. It seems that some press has been perhaps over promising the endpoints of this technology; however, it still remains that pharmacogenetics will potentially result in an 'evolution' not a 'revolution' in patient care (Sevilla 2004).

6.3 Example of a current clinical application: The TPMT case

There are a limited number of pharmacogenetic tests currently being performed clinically; none of which are the standard of care (Marshall 2003). Thiopurine methyl transferase (TPMT) testing is perhaps one of the most well known. It has been called "a perfect example of the promise of pharmacogenetic diagnostics, as individuals with an impaired ability to metabolize thiopurines are at risk of life-threatening adverse reactions" (p149 van Aken *et al.* 2003). Because of this, it will be described further in depth in this document as an example of pharmacogenetic testing.

This monogenic trait is in contrast to many of the polymorphisms of various drug-metabolizing genes, each with mild effects on phenotype (Ulrich *et al.* 2003). The risk of adverse effects with TPMT can be lowered by decreasing the thiopurine dose in individuals where testing revealed low activity of the metabolizing enzyme. Research has shown that individuals of European descent inherit TPMT alleles in the following ratios: 90% have high activity, 10% have intermediate activity (heterozygotes), and 0.3-0.5% have low or no detectable activity (Krynetski and Evans 2003, van Aken *et al.* 2003). However, allele frequencies are not so well known in other populations (van Aken *et al.* 2003, Sevilla 2004). Some thiopurine drugs are: 6-mercaptopurine (6MP), used in

the treatment of acute lymphoblastic leukemia (ALL); and azathioprine, a drug for immunosuppression after organ transplantation, as well as for patients with autoimmune diseases (van Aken *et al.* 2003).

There is currently a growing debate over the idea of mandatory genetic testing for TMPT before prescribing a thiopurine such as 6MP. Though thiopurines have been used for decades to treat ALL, the discovery of the *TPMT* gene on chromosome 6 in the mid-1990s and the subsequent development of a genetic test have changed how some doctors treat their ALL patients. Some hospitals in the United States, such as St. Jude in Memphis, Tennessee, and Mayo Clinic in Rochester, Minnesota, now genotype all their ALL patients before treating with 6MP. Others feel testing should not be mandatory, as now oncologists monitor their patient's blood counts vigilantly to monitor toxicity, and in that way would discover their patients who could not tolerate high doses of 6MP and be able to reduce the dose before dire consequences result (Marshall 2003). The current stance of the United States Food and Drug Administration (FDA) has been to discuss supplementary information for the product label with regard to TPMT metabolic activity and the potential for exposure to excessive bone marrow toxicity in pediatric patients with acute lymphoblastic leukemia. The proposal includes information to convey that only persons who have the homozygous condition are at high and consistent risk of developing toxicity, that preliminary data indicates that more than half of heterozygous persons tolerate standard doses, and that patients with normal TPMT status could still have severe toxicity Discussions have also included that the label be amended to indicate that tests for TPMT status are available, although no further recommendations on uses or interpretation would be given. At present no dosage adjustment recommendations are likely to be added to the label due to insufficient data being available to make specific doses recommendations (Pediatric Oncology Subcommittee 2003). In Europe, the labels also do not provide information on genetic testing; they currently state that a patient should be monitored by means of a red blood cell count (RBC).

The arguments on both sides are as follows...

Pro-mandatory *TPMT* genetic testing:

- If an adverse reaction was found, it would allow doctors to hone in on the drug that is causing toxicity, and reduce 6MP doses considerably, while keeping to a high level the other drugs that they can tolerate (Marshall 2003).
- This is known information that can save lives, and should not be withheld from clinicians (Marshall 2003).
- Blood counts during off-label thiopurine use for inflammatory diseases would most likely not be as vigilant (though noted to be "frequent enough" p. 590) as when used to treat ALL, so this could help out these populations earlier on in treatment (Marshall 2003). Furthermore, Clunie and Lennard (2004) have published an article stating the relevance of TPMT status testing for rheumatology patients.
- Current erythrocyte assays, which are the method most clinically used for monitoring TPMT activity, can have aberrant results if the patient had a recent blood transfusion (Krynetski and Evans 2003).
- For erythrocyte assays, the TPMT enzyme is stable for 3 days, however a 6-day-old sample has decreased TPMT levels. Therefore, the outcome of the phenotypic testing of TPMT activity in red blood cells depends on the handling of the blood samples prior to analysis (Lennard *et al.* 2001).
- Testing for the most common alleles, TPMT*2, *3A, *3C, account for over 95% of inherited deficiency of TPMT in a diversity of world populations (Krynetski and Evans 2003).

Anti-mandatory testing at the present time:

- Some disagree with the last 'pro-testing' point, and do not believe that the current testing investigates deleterious polymorphisms found in all populations. Currently most testing is focused on only 4 alleles that were discovered during early research: TPMT*2, *3A, *3B, *3C. Two additional alleles have been identified in other populations, TPMT*8 (African-Americans), and TPMT*6 (Asians); however, they are not thought of as 'classical mutations' so are therefore not commonly included in the panel of tests. If this test is going to be implemented in multi-cultural societies, then reliable data in all populations must be available – and that is not currently the case. More research is needed in this area (van Aken *et al.* 2003).

- Also, it seems that TPMT genotyping does not account for as many cases of adverse effects as TPMT activity assays. Though genotyping does catch individuals, and can save them from potentially life-threatening adverse reactions, it cannot identify all who will have adverse effects, so vigilant clinical monitoring will still be needed (van Aken *et al.* 2003). Some even go as far as to say that genotyping is potentially unreliable because of uncertainty in interpreting a novel polymorphism in various racial groups, as well as the possibility of missing clinically relevant allelic variation; phenotype testing instead is preferred (Clunie and Lennard 2004).
- High cost ($100-$300 USD/test) (Marshall 2003).
- There are no current standards on how to recalibrate drug doses once heterozygote results are known (Marshall 2003).
- Mandated prospective genetic testing may cause a delay in therapy, during the time that the test is performed and results are interpreted (Marshall 2003). The availability of a test result (turn around time) must conform to the clinical need.
- Will all physicians understand test results? Doctors may be overly cautious and either delay therapy or reduce doses too much if the results note a heterozygote – which is 10% of Caucasians. (Marshall 2003).
- Results may spread alarm and compromise therapy, and result in 6MP under-dosing (Marshall 2003).
- Conventional PCR genotype testing cannot distinguish between *1/*3A genotype (heterozygous since *1 denotes wild-type), and *3B/*3C genotype which is TPMT-deficient. A haplotyping method can help resolve this confusion; however, if not resolved this can pose a huge diagnostic problem (Krynetski and Evans 2003).

7 Potential economic impact

7.1 Costs of technologies

There are no hard data available on the economic impact of pharmacogenomics. As there are only a few clear cases of clinical use (ex: Gleevec, Herceptin, and TPMT), it is difficult to assess not just future but current costs and benefits (Sevilla 2004).

In the past 20 years, the costs of research and development of new medicines have steadily risen, while the number of new compounds entering the market has not (and has in fact seemingly decreased). Pharmacogenetics may help pharmaceutical companies innovate and increase the number of products in the pipeline. Also, pharmacogenetics may help this trend if companies can charge a high enough price for the resulting drugs, or if the development costs are significantly reduced given this change in focus of drug development (Sevilla 2004).

As far as investigating the cost-effectiveness of pharmacogenetic testing in the clinical setting, one could consider the following factors: "establishment of a link between genotype (molecular profile) and drug response; ease, rapidity and cost of genetic testing required; prevalence of the gene variants in question within the population; dominant versus recessive modes of inheritance; clinical and economic severity of the adverse reactions that might be avoided; and the potential for improved monitoring of drug response" (p751 Shah 2003). Veenstra *et al.* (2000) identified similar characteristics: the genetic variant is relatively common, a fast and inexpensive genetic test is available, a well established genotype/phenotype association exists, currently difficult to monitor drug response, and severe clinical or economic consequences can be avoided with pharmacogenetics. It was also felt that pharmacogenetic applications could be very relevant for medications with a high variability in response and a narrow therapeutic index, and that cost-effectiveness would be true only for a certain combination of characteristics, so should therefore be evaluated on a case-by-case basis (Veenstra *et al.* 2002).

The cost of technologies for SNP identification, or genotyping in a broader sense, becomes essential. It is necessary to analyse a tremendous number of individual DNA samples to clarify the relationships between a given genotype and a drug response. Genotyping such a high number of SNPs is currently not cost-effective. However, the cost of identifying one SNP from one individual has decreased in recent times, and currently costs

as low as $0.10 USD. To keep the costs down, to reduce it to $0.01, researchers are concentrating on multiplexing and mixing techniques (Roses 2002a). Focusing on the 60,000 SNPs in coding regions only and high-throughput techniques that allow faster and cheaper genotyping are favored. For a review of the approaches for genetic analysis, use of different markers, and emerging technologies for large-scale genotyping please refer to Elahi *et al.* 2004.

The widespread utilisation of SNP maps will become increasingly feasible as genotyping techniques become faster and cheaper and data from the HapMap provide insights into the minimal number of SNPs to genotype to capture the bulk of the common sequence variability in the genome (Johnson and Lima 2003).

Another technology that should be considered is that of DNA microarrays since they can be used to explore either variation in gene expression determining the individual phenotype, or variations in the DNA sequence such as SNPs (Meloni *et al.* 2004). Microarray techniques using tissue samples are a pharmacogenomic approach that is attractive where the relevant tissue for drug action is clear and easily accessible (as in oncology). However, in many situations, multiple organs or tissues are involved in the drug response and/or the relevant tissue is not readily obtainable from subjects. Thus, an SNP-based genomic approach is likely to be more broadly applicable in pharmacogenetics (Johnson and Lima 2003).

7.2 Quality management

Some state that there needs to be an even more comprehensive system to monitor benefit-risk profiles during clinical trials as well as during the post-marketing phase. This system will need to: collect and catalogue adverse events from clinical trials, from consumers or health care professionals, and from literature and regulatory authorities; gauge the seriousness of the reports; input all of this data into a database; medically evaluate the reports; analyze similar events for quick reporting to regulatory authorities; and make sure that timelines are kept for reporting to the regulatory agencies (Sayers and Self 2000).

Also, some feel that there would be a great unnecessary cost if there were no pro-active evaluation of the new diagnostic tools. Data should be gathered properly to obtain clear answers about the efficacy of new diagnostics (Gutman and Feigal 2003).

7.3 The drug development process

7.3.1 Pre-clinical research

Some studies state that a new drug takes 9-12 years to develop and costs approximately $608 million USD, with clinical development accounting for $263 million (Moldrup 2001). Some recent studies by Tufts University mention prices of $840 million per new drug (Tufts 2002) and an average of 7 years (Tufts 2003). Figures like these have however provoked scepticism in certain public groups (Public Citizen 2001). Pharmacogenetics may enable the pharmaceutical industry to enhance the productivity of drug discovery and development, shortening the time and the costs required, eliminating the waste of time and money in some of the clinical trials with large number of patients, long durations and high failure rate (Jain 2003).

The initial commercial impact of pharmacogenetics could be on the safety of marketed medicines. Therefore, the objective in research would be to identify a genetic profile that characterizes patients who are more likely to suffer an adverse effect, compared to those who are more likely to respond optimally to the drug. Clear return of investment may be maximized by the ability to limit use of the medicine to those who are not at risk of uncommon adverse reactions (Roses 2002a). If pharmacogenetic predictors of adverse events could prevent the exposure of genetically vulnerable patients and so preserve even a single drug in the pipeline, the cost of any large-scale research effort could be fully recovered (Goldstein *et al.* 2003).

7.3.2 Clinical trials

In trials that utilize genetic testing as a screening tool, the number of individuals to be followed during the trial could eventually decrease under well defined circumstances. Some estimate that the number of patients needed in Phase II trials could be reduced by 50% and by 10% in Phase III. In addition, the time required to complete

Phase III could be reduced by 20%. This could result in overall cost savings of as much as $500 million per drug launched (Ross and Ginsburg 2002). However, more people would need to be recruited overall, to screen for the wanted genotype. It has been suggested that the allele frequency in the population, as well as the type of gene action (i.e. dominant, recessive, or additive) and effect size, will affect the number of participants needed in the trial – perhaps by orders of magnitude (Cardon *et al.* 2000). If individuals are easy to recruit, and the wanted genotype is of a high frequency, such screening should not be cost-prohibitive (Fijal *et al.* 2000). However, the genetic epidemiology needed as a next step is a time consuming and costly exercise (Sevilla 2004). The genetic tests themselves will increase costs, however, expectations that the cost savings gained from fewer participants may be more substantial. It is estimated by some authors that the likelihood of reducing the total cost in most situations with high per patient cost is high while the cost of genotyping is low (Fijal *et al.* 2000).

Clinical trials could become cheaper, and smaller if researchers would only have to recruit patients with the appropriate genotypes for inclusion. Some claim that pre-screening by genotype is similar to current traditional screening such as measuring cholesterol levels to ensure that the participants are at a certain cut-off, etc; therefore reducing patient variability and making it easier to show an effect with a smaller sample size (Fijal *et al.* 2000). Time will tell if this is utilized, as it assumes up front that one will know that the drug will only be effective in a subpopulation. Currently it seems that some (but not all) pharmaceutical companies predominantly pursue pharmacogenetic research if a bimodal response is noted, i.e. pharmacogenetic research is initiated only if variability in clinical outcome (safety and/or efficacy variables) is observed and a pharmacogenetic hypothesis can be proposed. If certain genetic polymorphisms are then found to be associated with the response, then subsequent research may take into account such findings. At this stage, however, it was pondered whether there would be enought solid data to develop an effective test (with an appropriate positive/negative predictive value, specificity and sensitivity). Some pharmaceutical companies reiterate that they are not specialized entities to develop genetic tests, but see that as a means to possibly make some of their compounds marketable (Sevilla 2004).

If there are fewer participants in the trials, who are then also less genotypically diverse, then some note that there is a greater risk that potential side-effects in the total patient population will go undetected (Moldrup 2001, Rothstein and Epps 2001, Thomas 2001). This may lead to unfair representation in trials, as well as a loss of benefit of participation to individuals who would have otherwise been able to join. Also, it could cause a reduction in the number of participants, and therefore could affect the validity and applicability of the test in the clinical setting (Issa 2000).

Statistical significance with a small sample size does not automatically relate to clinical significance, as screening has implications for how far the results can be generalized (Fijal et al. 2000, Issa 2002). A drug could therefore potentially go into the market with less information known about it, than if it had gone through a clinical trial by today's current standards. Post-market data collection, recording, and analysis on the part of both regulators and industry will become important (Rothstein and Epps 2001, Thomas 2001).

The reduction in sample size could be viewed on a positive note, however, from the point of view of the participants - it would help exclude individuals who are less likely to reach the hypothesized endpoint of efficacy, and therefore would lessen their exposure to potentially toxic treatments (Fijal *et al.* 2000, Shi *et al.* 2001).

It may also be important to take into account multicenter genetic variability when pooling data from multicenter/multinational clinical drug trials, as data interpretation from Phase I can influence dosage decisions in Phase II, etc. (Issa 2002).

The Pharmacogenetic Working Group developed elements of informed consent specifically relevant to pharmacogenetic trials (please see Anderson *et al.* 2002). Participants are to know information regarding benefits and risks of enrollment (Rothstein and Epps 2001). Evidence of some genetic variation may "lead to individuals being classified as 'difficult to treat', 'less profitable to treat', or 'more expensive to treat.' The fear of being so classified could act as a barrier to the recruitment of research participants" (p229 Rothstein and Epps 2001).

Stratification for trial participation brings to light that potential problems can result due to penetrance issues. "The variable degree of the clinically relevant phenotypic expression of genetic variation could lead to false positives...[also] some participants might not be offered the opportunity to receive trial medication if the given polymorphism in question is present, but [the effect] is not highly penetrant...Will a given drug be restricted to patients with a particular polymorphism, even though individuals in the larger population might present with variable degrees of penetrance [or expressivity]?" (p305 Issa 2002). More investigations need to be performed on polymorphisms with only mild or inconsistent effects on adverse effects and drug response (Issa 2002).

An additional consideration is whether to include economic evaluations alongside clinical trials. There is some resistance to the idea in certain communities that economic evaluations should be done alongside clinical trials, however, by the time the trial is over, it could be that the intervention the trial has been testing may not be cost-effective. If a company/health service knew that the drug was going to be too expensive due to the cost of therapy, etc., early on, it may save money in the long run (Adams et al. 1992, Drummond 1994, Luce and Simpson 1995).

7.3.3 Marketing

There may also be an increased market potential, as clinicians and patients will have an increased confidence in these drugs, ideally leading to reduced trial-and-error in prescribing, and greater patient completion and compliance; "a drug that is guaranteed to work for everyone for whom it is prescribed is more likely to command a premium price" (p208 Moldrup 2001).

The bottom line seems to be a delicate balance: if payers are reluctant to pay more per drug for the expected increase in benefits, and/or if testing reduces populations eligible to be prescribed the medication, but the reduced costs of R&D are not reduced enough to compensate, then commercial development may not be viable (Danzon and Towse 2002).

"Increased cost-effectiveness could result from more efficacious treatments with better quality of life, lower costs from smaller trials, fewer errors in prescribing and the ensuing higher rates of completing the full course of medication, and decreased ADRs" (p751 Shah 2003), as well as by the greater specificity of drugs and therefore greater expected health gain per person (Danzon and Towse 2002).

For a detailed analysis of the economics of pharmacogenetics, please refer to Danzon and Towse (2002).

7.4 Healthcare system

Pharmacogenetics could be used to improve patient therapy, aiding in how drugs are selected and prescribed. For health care, the expected positive impacts are to improve health outcomes for patients and to reduce the overall cost of disease management for the individual. Two main advantages:

- Minimized adverse effects: Hospitalization and deaths and financial burden from adverse reactions is currently very high. Some state that adverse effects are responsible for 7% to over 10% of hospitalizations in some European countries with an average cost of $2000-$3000 per incident (Wilkins 2002, Abbott 2003).

- Improved therapeutic efficacy: Many current mainstream drugs show only limited efficacy in as many as 70% of treated patients. As many as 20-40% of people receiving pharmacological agents may be on a drug which is not effective for them. Even the most effective therapies do not work in 20% or more of the treated patients (Spear 2001). Pharmacogenetics is projected to result in safer, more effective and more cost-efficient medicines (Roses 2001a).

It is not currently possible to evaluate the wide economic impact of pharmacogenetics on health care systems. Lower test costs are possible with higher throughput and more automated testing systems, but the cost of labor,

overheads, supplies and profit must still be included (Wedlund and de Leon 2001). There will be an expected increase in expenses of associated devices like gene chips but also a reduction of the overall cost of disease management for the individual. The synergy of lower trial costs and efficacy-based prescription could lower the drug bill per medicine (Roses 2002b).

Pharmacogenetics could contribute to a more targeted and cost-efficient preventive treatment. Current payment systems do not encourage more streamlined prescription protocol, since trial-and-error methods result in more office visits (Moldrup 2001). Some argue that overall healthcare will become cheaper because the amount of physician-visits will decrease with pharmacogenetics in practice. It is, however, expected that patients will still need to be clinically monitored, if they are tested or not (van Aken *et al.*2003, McNally *et al.* 2004, Sevilla 2004).

Pharmacogenetics could also result in increased costs for health care systems. If pharmacogenetics falls in the category of high volume/high cost medical treatments, there will be concerns from health care managers over the justification of its use. Another point of interest is the possible advantage to be gained by private health care organizations over the competitors if they are the first to offer tailored health care to their customers.

How will the emergence of pharmacogenomics impact on public health? While some argue that genomics will provide additional tools to combat disease, "an emphasis on genetic factors may divert attention from health improvements that can be made through social and economical actions" (Moldrup 2001).

8 Potential consequences for different stakeholders

8.1 The pharmaceutical industry

Pharmacogenetics may enable the pharmaceutical industry to adopt a novel approach to drug discovery and development. A strategy for searching for therapeutic targets is very difficult to evaluate (Alhenc-Gelas *et al.* 2003). Nevertheless, this means of drug discovery may allow for a more comprehensive approach, accelerated screening, and new insights on targets.

From the perspective of a pharmaceutical company's marketing department, subdivision of an existing market into smaller pieces is not an ideal business practice (Rothstein and Epps 2001). Some companies may be resistant to change their focus from developing one hugely profitable drug, to multiple drugs directed towards small target populations (Moldrup 2001, Phillips *et al.* 2001, Buchanan *et al.* 2002). On the other hand, a company may end up with smaller but exclusive markets without having to fear generic competition, and this may be economically more attractive (Jain 2003). "In the long term, economic limits to stratification may also be partially balanced by better completion of drug regimens and increased revenue owing to more product approvals. However, if a single company was not able to develop drugs for all segments of its existing market, as is plausible, the revenue loss would be considerable" (p748 Shah 2003).

In general, companies would prefer to invest large amounts of money into drugs that will treat large amounts of people. Therefore, some predict that industry may direct their resources towards developing drugs for individuals with the most common genotypes (Rothstein and Epps 2001).

A potential advantageous aspect of the pharmacogenetics field for industry is that it may allow some drugs to be developed that may have been unsuccessful without stratification by genotype. Some authors have suggested this may enable some medicines to be resubmitted that previously failed during development or in the early post-launch phase (Moldrup 2001, Phillips *et al.* 2001, Shah 2003). Although, genotyping could help reduce the pool of people who had adverse reactions to the drug, thereby increasing the chance of (re)approval, this strategy would need to have a positive impact on the overall risk/benefit evaluation of the medicine and be acceptable to the drug regulatory authorities. Furthermore, there would have to be another investment in time and money in discovering an appropriate genetic screen and then redeveloping the drug. This will further reduce the time the product would be protected through patents, thereby reducing the company's opportunity to recover their front-

end costs. Regulators will also presumably impose additional stipulations and studies, thereby limiting incentives to seek re-approval. Given this, time will tell if companies truly will seek this opportunity (Shah 2003).

Pharmacogenetics may also speed up the time needed for global approval of pharmaceuticals. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (www.ich.org) recommends that countries necessitate clinical studies to be performed on their own populations before licensing foreign-tested medicines (Shah 2003). By using pharmacogenetic research to show that different populations metabolize a drug in the same way, then the need for complete clinical studies may be circumvented. (Hodgson and Marshall 1998). On the other hand, things are more complex if a drug is submitted for approval in a population where new genetic variants are found, or where the prevalence of relevant variants differs from other countries where clinical trials have already been completed.

Also, economic considerations of pharmacogenetics drive a differentiation between the research focus in industrial and academic sectors. Therefore, there is a need to establish appropriate structures that would facilitate the transfer of research projects and information between industry and academia research sector (Goldstein *et al.* 2003, Sevilla 2004).

Different pharmaceutical companies have different agendas on how they utilize pharmacogenetics in their drug development. It seems that most companies gather blood samples in current clinical trials – however, the differences lie in how and if the DNA of these samples is investigated further. Many academic researchers see the opportunity for industry/academic partnerships to utilize this great resource of samples; however, additional questions lie in how consent and anonymization could occur for this to happen in the future (Sevilla 2004).

In utilizing pharmacogenetics in research, some pharma companies focus their efforts on drug safety, whereas others are more focused on efficacy. Some endeavor to use their collected data to help as early on in the decision-making process as possible, in order to address the issue of attrition. Others focus their research efforts on trying to better classify disease and disease pathways, to therefore gain better insight into how to identify drug targets. Generally, prospective genotyping is mainly done only if mandated by regulatory bodies. These are only the viewpoints of a few companies, however, and other companies may have different strategies. A request of researchers is to have greater transparency in the inner-workings of industry – and to have it be on an equal level for all companies to make sure proprietary issues are not compromised (Sevilla 2004).

8.2 Healthcare providers

It is possible that high throughput screening may make genetic testing much easier, resulting in the dissolving of the connection between specialized molecular laboratories and genetic counselors. Interpretation of the test results is therefore increasingly likely to be performed in primary care as well as by specialists and doctors from many medical disciplines. Due to this, it will be important to educate clinical laboratories of their needed expanded role, including the vigilant gatekeeping needed to make certain the correct test is ordered, informed consent obtained and upheld, and test interpretation maintained (Grody 2003) as well as educating health care professionals to make sure they are fully aware of which tests to order, and how to handle the results once they have been received.

What is not currently in place is the framework of genetics education for all physicians – without which is it unlikely that they will be able to quickly and accurately integrate pharmacogenetic testing into their practice (Buchanan *et al.* 2002, Shah 2003). "One significant factor yet to be accounted for is the role of clinicians, who have been trained to diagnose on the basis of symptoms and morphology rather than stratification based on molecular features (p748 Shah 2003)." Physicians may be a limiting factor in the safe and effective use of pharmacogenetic drugs in clinical practice (Melzer *et al.* 2003).

To competently practice medicine in the future, physicians will need to be thoroughly educated in genetics. Also, "doctors need to be aware of whether a drug they are prescribing is subject to pharmacogenetic variability without taking it for granted that genetics play the main role in determining a patient's response to treatment"

(p378 Mordini 2004). Given that a multitude of factors besides a person's genetic make-up determines how an individual will respond to a drug, physicians will need to be able to use their professional judgement to decide if they should use a genetic test to determine drug dose, as well as how much they will use the test result to influence their decision (Buchanan *et al.* 2002, Shah 2003). General practitioners are poorly prepared to handle these issues, as are many other health professionals (Moldrup 2001, Grody 2003); pharmacists also have a lack of knowledge in this area (Moldrup 2001).

Currently, several medical schools in both Europe and the United States are working towards incorporating pharmacogenetics into their curriculum, however the number of those that offer actual classes on the topic (or even on genetics or molecular biology) is quite small. Those that do are geared towards non-medical students, since rigorous medical school curricula do not easily accommodate additional coursework (Gurwitz *et al.* 2003).

In clinical practice, a team approach will be quite important due to the complexity of this kind of optimized therapy (Moldrup 2001). Division of responsibilities could be envisaged, such that physicians could be responsible for prescribing a class of drug, whereafter pharmacists could use the genetic results of the patient to determine the correct sub-type of drug, as well as the dosage – in cases where there is a well-defined pharmacogenetic effect that would not need balancing with other medical information (Shah 2003). The Royal Pharmaceutical Society of Great Britain feels that pharmacogenetic testing could have the greatest benefit for patients when the pharmacist works closely with the patient and the independent prescriber (Nielson 2003).

"With greater knowledge comes greater responsibility" (p230 Rothstein and Epps 2001). Physicians and pharmacists may be subject to liability if they are not fully knowledgeable about the applicability of certain genetic tests to certain prescriptions, or do not know how to alter dosage appropriately, based on pharmacogenetic test results (Rothstein and Epps 2001).

Physicians could be duty-bound to offer a pharmacogenetic test if the benefits outweigh the risks in doing so. This is most likely to occur when a test has a high positive predictive value, and the results can be easily translated into how to prescribe a certain drug (i.e. if the drug should be prescribed at all; if so, the dosage; and how to prescribe it in combination with other drugs) (Buchanan *et al.* 2002).

However, once the test results have been received, how much freedom will be given to the physicians who wish to prescribe a medicine with known pharmacogenetic restrictions? If the test has low predictive power, will the physician be sufficiently educated about this fact, and be given the freedom to prescribe the drug though the test suggests otherwise? If the patient has been informed of their potential risk of side-effects and consents to receiving the medication, then the physician will have fulfilled their duty (Buchanan *et al.* 2002).

8.3 Patients

Pharmacogenetics could lead to an individual's self-knowledge of a part of his/her genome, which may be a responsibility that not all individuals are willing to take on (Moldrup 2001). However, once individuals are given this knowledge, they could increase their demands to the health care system for information and advice for treatment. Therefore, quality and equity of access will need to be upheld as well (Moldrup 2001). One can expect that restricted availability (and/or reimbursement) of medicines for certain subpopulations may negatively impact patient/ physician relationships. Also, poorly communicated and/or understood genetic information may give rise to anxiety or unjustified fears with serious complications. The experience with the first generation HIV tests, which had a relatively high false positive rate, may serve as an example.

For further description of how pharmacogenetics may affect patients, please refer to section 9: "Potential consequences for society and individual patients."

8.4 Health insurers

With their reimbursement policies, insurers play a large role in the use and dissemination of new medical technologies in some countries (Schoonmaker *et al.* 2000). Some feel that private insurers may potentially cover only treatments that have minimal risk based on pharmacogenetic tests (Moldrup 2001, Shah 2003). However,

in regards to genetic test results and policies, private insurance companies say: "the reality is that competitive pressure to increase sales already prompts most companies to accept, rather than avoid, marginal risks" (p196 Nowlan 2002).

It is suggested that genomic screening may redefine the term 'pre-existing condition' for insurance companies (Grody 2003), and if an individual is found to have a genotype that would characterize them as difficult or expensive to treat, they may be discriminated against by health insurance providers (Thomas 2001, Shah 2003). Because of this worry, over 28 states in the United States have enacted legislation prohibiting insurer's use of genetic information in pricing, issuing or structuring health insurance, and similar trends are happening in Europe (Hoy *et al.* 2003). Though not specifically addressing pharmacogenetics, most of these laws prohibit discrimination against asymptomatic individuals who are genetically predisposed to disease, and the laws may not apply once the individual becomes symptomatic. However, some feel the enactment of such laws is a reaction of an 'alarmist' mentality, since it is addressing a problem that individuals are not currently facing and is largely theoretical (Nowlan 2002, Hoy *et al.* 2003).

With pharmacogenetics, there could be both a rise and lowering in costs for insurers. There could be savings in potentially less claims filed, due to increased efficacy as well as fewer adverse reactions, and therefore higher compliance rates. However, there could also potentially be higher costs due to expensive drugs from smaller markets, and a need for genetic tests before prescriptions can be made. Insurers may regulate very expensive drugs by mandating pre-prescription genetic testing before they will reimburse (Shah 2003).

"This could theoretically lead to a perplexing scenario where, from the point of view of an insurer, an individual with a low probability of manifesting a disease but a poor predicted response to treatment would have a similar or even higher risk, than someone with a high probability of manifesting the disorder but a good chance of appropriate response to treatment" (p752 Shah 2003). However, it is also true that risk assessment in health care insurance is more complex than this implies; much more than two inputs are involved in the calculation of premiums (Sevilla 2004). "The impact of a positive test result is very often overestimated: as with other, conventional medical data, genetic tests can only be interpreted in risk assessment in probabilistic terms and not in terms of certainty" (p 42-3 Bürger and Regenauer 2004).

Raithatha and Smith (2004) believe that in the future, tests for phenotype (e.g. high blood cholesterol test) and tests for genotype (e.g. genetic test predisposing to an increased risk for heart disease) should be able to be treated the same in regards to insurer use. In this example, they argue that the statistical risks of both to heart disease could be based on population studies, and therefore should be able to be used the same way in an actuary analysis. They feel that once the predictive power of a genetic test has risen to an appropriate level, it would be more suitable to use it in this manner, since currently it is mostly inappropriate (but not unethical) due to the shortage of information linking genetic status, lifestyle and future health. They, however, did not extrapolate to pharmacogenetic testing.

The European Society of Human Genetics, Professional and Public Policy Committee has previously composed a document and recommendations on "Insurance and employment: Technical, Social and Ethical Issues." Please refer to http://www.eshg.org/PPPC.htm

8.5 Policy makers

'Orphan medicinal products' is a name currently used to signify medicines that treat rare diseases. As they are targeting a small patient group (i.e. less profitable) policy makers around the world have offered economic incentives for their development. Could this be the fate of pharmaceuticals geared towards individuals of less common phenotypes? (Rothstein and Epps 2001, Issa 2002). It seems likely, since Gleevec and Herceptin both sought such a designation (Shah 2003). Some pharmacogenetic drugs potentially share many common traits of traditional orphan drugs such as: aiming towards small affected groups where there currently is a lack of effective treatment, targeting treatment of serious diseases, a fast development phase with fewer trials with less patients, and backing from regulators (Shah 2003).

With the future pointed towards increased market segmentation... "It is likely that entire populations might be given minimal attention in such market-driven drug development, which would result in 'orphan populations'" (p305 Issa 2002). Regulations should be made that address both the orphan drug and orphan population issues (Buchanan *et al.* 2002, Issa 2002, Melzer *et al.* 2003).

"From a legislative perspective, however, the rising level of tax credits [relevant for the United States, but may vary according to member states in the European Union], non-negotiated pricing resulting in high prices and financial subsidization that orphan drugs enjoy may become difficult to sustain in the long term" if pharmaceutical companies apply for orphan status for all pharmacogenomic drugs..."The most common reason for the denial of orphan designation is because of disagreements over how target populations are defined" (p749 Shah 2003). In the United States and Europe, Gleevec was successful in this endeavor (Shah 2003); however, in the U.S., Herceptin was denied orphan status for breast cancer though was granted this designation for the subset of pancreatic cancers that over-express HER2.

8.6 Regulatory bodies

There are technical and societal issues associated to pharmacogenetic testing in clinical setting to be further discussed and addressed in public (and in health planning) to build upon competence and trust. Among them should include the development of "good practices" in genetic testing, and provision of valid information, quality assurance, availability and accessibility of tests and test centers (Sevilla 2004).

Other requirements could be enhancement of pre- and post- approval monitoring (validation of pharmacogenetic markers and associations with clinical outcomes). An important need is the continued education of health professional and public health managers, and increased patient information. An effort should be made to adapt public health infrastructures and pharmaceutical market dynamics (Sevilla 2004).

Some potential regulatory issues are with generics already in the market, where prescribing could be impacted by new pharmacogenetic information (differential efficacy, identified individuals for potential adverse effects, etc). There could be legal issues on liability, on competitivity (can it be made compulsory to re-evaluate drugs already in the market if a new pharmacogenetic test is released?). Other challenges will be to ensure access to the pharmacogenetic test (which might be different from the access to the drug), and the availability of information (physicians already used to the product might not be aware of new test), etc. (Sevilla 2004).

Another potentially conflicting scenario that pharmacogenetics might lead to is the identification of a new claim for an old product. This will cause identical products in the market confronted with different requirements (Sevilla 2004).

As both medicines using pharmacogenetic information and genetic testing will be closely linked, regulatory agencies dealing with these should have relevant expertise in drugs, tests/devices, and genetics. The United Kingdom recently merged its Medicines Control Agency and Medical Devices Agency, so that the departments responsible for licensing of new medications would be connected with those overseeing tests (Shah 2003). Regulatory agencies will need to know the science of the drug, as well as the science of the corresponding genetic test, and if they will work together effectively (Hodgson and Marshall 1998).

As mentioned previously, The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (www.ich.org) brings together regulatory officials from various jurisdictions. Also, the European Agency for the Evaluation of Medicinal Products (http://www.emea.eu.int), as well as the United States Federal Drug Adminstration (www.fda.gov) continue to develop guidelines specific to this area. Please refer to Appendices I and II for a listing of relevant international and national regulatory frameworks.

9 Potential consequences for society and individual patients

9.1 The issue of testing

9.1.1 Testing for polymorphic sequence variants compared to genetic tests for monogenic disorders

In common: familial implications
SNP results within coding regions could also relate to disease susceptibility, and thus have much further implications for the individual, as well as other family members with a risk of carrying the same polymorphism. In addition, there is the potential of revealing non-paternity if multiple family members are subsequently tested (Robertson 2001).

Some advocates of pharmacogenetics note that there should be no cascade screening with pharmacogenetic tests (not linked to disease susceptibility), as they would only be appropriate if another family member would need to take the same medication. However, as it is surmisable that polymorphic variants associated with drug response could also be associated with other types of susceptibility to disease, it is reasonable to conclude that cascade screening would be appropriate in these cases (Sevilla 2004).

Difference: conditional risk
Also, as discussed previously, there is a "broad distinction between disease alleles (rare alleles with strong health effects) and susceptibility alleles (common alleles with weak effects)...a single allelic variant [can be] one component in a web of factors that lead to disease...gene-gene and gene-environment interactions presumably have a strong role" (p362 Wilcox *et al.* 1999).

9.1.2 Information about genetic susceptibility compared to other medical information

In common: element of the medical work-up
Some feel that genetic testing for a monogenic disease can have psychosocial consequences that must be considered; however, they do not feel that drug-response genetic testing should automatically be considered to have the same impact. Instead, "...medicine response tests will provide information directly related to a participant's likely response to a specific medicine; they are comparable to other laboratory tests such as drug concentration monitoring and liver enzyme analysis" (p269 Renegar *et al.* 2001). In this way, some pharmacogenetic testing may not greatly differ from other types of testing in clinical practice (Sevilla 2004).

Difference: negative perception of mutations/ fatality/ familial implications
However, others feel that "genetic information is more vulnerable to violation of privacy because it contains an individual's probabilistic future diary." (p209 Issa 2000). Pharmacogenetic testing could potentially be more than just a single intervention, since the information collected may be predictive of future events, or affect other family members (Buchanan *et al.* 2002, Grody 2003).

It is possible that stratification of individuals may create a new category of sub-clinical 'conditions;' such that healthy individuals might label themselves 'ill' given that they have a certain drug-associated genetic polymorphism (Issa 2002).

Moldrup (2001) posed the following questions: should all individuals be screened to see if they will appropriately respond to therapy? If the individual has a genetic profile that has no corresponding appropriate therapy – what is the point of even diagnosing the problem? In this author's view, it does more harm than good to diagnose an individual when no treatment is available - which is the reason for the ever increasing number of chronically ill individuals (Moldrup 2001).

It is important to not confuse the predictive value and information generated by the test with the nature of the test, i.e. that the information content of the result is more important than which test was used to generate that information (Nuffield Council on Bioethics 2003, Sevilla 2004). All medical data (including genetic data) must satisfy equally high standards of quality and confidentiality, and 'genetic exceptionalism' should be avoided. However, the public perception that genetic testing is different needs to be acknowledged and addressed. The

type of test used is not a trivial matter, since some people perceive the results of genetic tests to be more accurate than other means of tests with the same endpoint result. This in turn could feed into their perceptions of risk, and how they choose to proceed with medical decisions. This highlights the need for greater understanding of the nature of genetic susceptibility and the probabilistic nature of pharmacogenetic tests (Sevilla 2004).

9.1.3 Information revealed by drug-use compared to information revealed by pharmacogenetic drugs-use

Post-marketing issues will need to be openly discussed. Currently, drugs, and the individuals that take them, can be viewed by the public in a much more open way than genetic tests and their results, which are kept in a different realm of privacy. With the advent of drugs targeted for specific, pharmacogenetically defined subpopulations, there is a possibility of stigmatization or discrimination on just possessing these drugs, since they could immediately and directly reveal information about their genotype. For instance, methadone and disulfiram users are stigmatized as drug users and alcoholics. Particular pharmacogenetic drugs [cardiac medications, anti-psychotics, etc.] may become a marker of individuals' genetic predispositions – so how does society deal with this genetic information becoming more openly accessible? (Moldrup 2001). "It is questionable whether it is possible to regulate and make guidelines for how people handle their drugs and related information sources (e.g. the prescription, the receipt, the health insurance bill) after they leave the general practitioner, hospital or pharmacy" (p211 Moldrup 2001).

9.2 Accessibility to pharmacogenetic testing

9.2.1 Denial to at-risk persons

Stigmatization of poor drug metabolizing individuals could result in a barrier to drug treatment (Moldrup 2001). This could also be true of individuals who are part of a group where there is a large ratio of "poor drug metabolizing individuals" i.e. racial groups, geographical groups, etc.

Many articles state that pharmacogenetics will allow physicians to "precisely prescribe or design the right drug, at the right dose, for the right patient" (p594 Shi *et al.* 2001). It is true that some uses of pharmacogenetics may be only to adjust dosing regimens; however, what happens if the 'right drug' has not yet gotten approved for use, and only the 'wrong drugs' (according to his/her genotype) are available? Will the patient be deprived of them? A threshold will need to be made, but this would hope to be lowered for an individual with a serious condition for which there is no other alternative treatment. Denial of care is not an effective option (Sevilla 2004).

9.2.2 Denial to persons not consenting to be tested

Regulatory agencies may mandate pharmacogenetic testing before prescription of related drugs could occur. However, if an individual chooses not to proceed with the genetic test, due to the variety of reasons delineated above, they may not be able to be prescribed that medication. What if that is the only medication available for them? Indeed, can true consent be received when there is really no other option?

9.2.3 Cost as a barrier to access

As new technologies are expensive when first introduced, laboratories may not be given adequate reimbursement from third-party payers. Therefore, if an individual cannot pay the difference, they may be denied access (Rothstein and Epps 2001, Grody 2003, Shah 2003).

9.2.4 Developing countries

Some question if individuals in developing countries will have the same access to pharmacogenetics as those in developed countries. Currently, the magnitude of other issues are so high as to not put human genomics research or its applications on the agenda of most major international health agencies (Weatherall 2003). It seems that pharmacogenetics could have a greater impact in developing countries through the application of the technology on the genotyping of pathogenic organisms, and not the human host *per se* (Pang 2003). Accurate diagnosis in infectious diseases is important, and taking this into account an expert panel ranked "modified molecular technologies for affordable, simple diagnosis of infectious diseases" as the number 1 biotechnology among the top 10 biotechnologies for improving health in developing countries (Daar *et al.* 2002). Also, for the full

potential of genomics-based health care to be realized in these countries, richer countries will have to change their emphasis in education and research to have a more global view of disease and its consequences (Pang 2003, Weatherall 2003). Otherwise, "the widely held fear that the fruits of genomics will simply widen the gap in health care between rich and poor may become a reality" (p598 Weatherall 2003).

9.3 Data storage and confidentiality issues

For whatever reason a genetic test is performed, privacy through security and confidentiality is essential. For some predictive genetic tests, results may be given to the patient only, and not put into the medical record, or a patient's genetic information could be kept on files of several health care providers. It will be crucial to have a proper maintenance of strict confidentiality of this information, like is to be expected for all sensitive medical and personal information (e.g. HIV tests). Security will have to be even more sensitive for electronic hospital records (Grody 2003).

Robertson (2001) and Buchanan *et al.* (2002) note that besides legal protection of genetic samples and genetic test results, other methods of storing information could be useful in the goal to protect privacy and confidentiality. One way could be to create 'firewalls' between the data and non-authorized individuals. This could be done by putting only the interpretation of the test results in the medical record (i.e. if a drug could or could not be prescribed), instead of the actual genetic profile (Robertson 2001, Buchanan *et al.* 2002).

Some pharmacogenetic tests will consist of testing only one gene. However, if genomic screens such as microarrays become automated for large-scale use, it could entail data storage in enormous institutional information systems. It is also quite possible that the complexity of such results would mean that no one report or counseling session could truly convey all the results. Therefore, one may have to repeatedly refer to the database to harvest information – but if this becomes the case, where should the database be housed, and who should have access? (Grody 2003).

Some feel that regulations to protect from the unauthorized release of genetic information would be good, but not sufficient to protect confidentiality and privacy, since powerful third parties could mandate that the individual authorize the release of the records to them. They (employers, health or life insurance companies, mortgage company, etc.) could lawfully obtain the information, and then subsequently misuse it (Rothstein 1998).

The European Society of Human Genetics, Professional and Public Policy Committee has previously composed a document and recommendations on "Data storage and DNA banking: quality issues, confidentiality, informed consent." Please refer to http://www.eshg.org/PPPC.htm

9.4 Patient education and informed consent

Some believe that the risk of psychological harm to the patient should be weighed, and if assessed to be of low-risk, pharmacogenetic tests could be treated like other laboratory tests, i.e. with minimal explanation. However, if found to be high-risk, then the risk should be disclosed to the patient and explicit consent from the patient should be received before proceeding. Ways to reduce this risk include: pre- and post-test counseling, patient education about genetics and pharmacogenetics, other potential unrelated information gleaned from the results, physicians' ability to keep test results confidential (and potentially firewalls in place to help this), and policy that prevents discrimination on the basis of the results. Also, if tests are designed to have minimal secondary information, this risk could be reduced as well (Buchanan *et al.* 2002, Nuffield Council on Bioethics 2003).

In general, there is a clause in informed consent for the right of the individual *not* to know the test results. However, in a pharmacogenetics context this seems contradictory since this clause is not applicable when a test is conducted for the purpose of drug selection. The question of whether to respect the right "not to know" in this circumstance is not yet solved (Sevilla 2004).

Some experts feel that there should be increased research into public engagement, as there is a danger of the deficit approach to public education about pharmacogenetics. Also, patients and the public have real anxieties about particular applications of genetic tests. The potential benefits of pharmacogenetic testing will only be realised if the public is engaged with the process (Sevilla 2004).

9.5 The provision of currently unknown information

As discussed in section 9.1.2 some believe that it will be important to not promote 'genetic exceptionalism' or 'overbroad genetic generalization' when discussing the interweaving of pharmacogenetic tests into the mainstream. Their feeling is that all genetic tests do not raise the same ethical issues, and thus should not all be required to have the same special regulations (Buchanan *et al.* 2002, Sevilla 2004). However, when pharmacogenetic research utilizes information previously gathered from genes involved in disease susceptibility, it could be true that pharmacogenetic tests overlap with diagnostic genetic tests; i.e. a result on a pharmacogenetic test could point to which drug is optimal, but could also give information into the prognosis of disease (Goldstein *et al.* 2003, Hedgecoe and Martine 2003). For examples, please see table 1 of Hedgecoe and Martin (2003). This is not necessarily limited to the disease being treated, for instance the apolipoprotein A4 allele (*APOE4)* is associated with a lesser response to statin treatment for lowering cholesterol, as well as an increased risk of Alzheimer disease (Goldstein *et al.* 2003).

Angiotensin-Converting Enzyme (ACE) is another example of a pharmacogenetic test that could provide more information than just drug response. Research has noted that the I and D alleles of *ACE* are possibly associated with interactions with β-blocker therapy (McNamara *et al.* 2001) as well as with the drug sildenafil (Eisenhardt *et al.* 2003). However, it has also been noted that these alleles could give insight into physical performance (Montgomery *et al.* 1998, Scanavini *et al.* 2002).

It would be quite difficult to limit genetic testing to only providing results on the pharmacogenetic issue at that moment (Moldrup 2001). Even if there is currently no overlap, it is always possible that a variant that today is know to be associated with drug response will at some future time be discovered to be associated with disease predisposition (Moldrup 2001, Goldstein *et al.* 2003). In this way, pharmacogenetics may not be totally exempt from the ethics discourse involved in genetic testing. Some feel that this should not prevent the use of a test with proven current clinical use, but others feel that it should always be at the back of one's mind when discussing this topic (Sevilla 2004).

Incidentally, pharmacogenetic testing may in fact become completely identical with genetic testing for a monogenic disorder. Genetic testing for *SMN1* deletions and gene conversions in patients suspected of having spinal muscular atrophy also reveals the copy number of the *SMN2* gene, determining in part the success rate of valproic acid treatment (according to recent research by Brichta *et al.* 2003), and thus the results from initial diagnostic testing could potentially also be used for prediction of drug treatment outcome.

10 Public perception

10.1 Distortion of perception of genetics

The public is aware of familial risk factors to complex disease, for example, the knowledge that a family history of heart disease raises the likelihood that others in the family could develop it too. However, a genetic test seemingly points more to the individual instead of the group, and is perceived to be more accurate and determining (Levitt 1999). "Public attitudes of genetic reductionism, the idea that individuals are defined exclusively by their genes, might be exacerbated by an overemphasis on pharmacogenomics, and should be disputed" (p752 Shah 2003). Education of the public will be needed "to guard against the powerful lure of belief in 'one gene one response'...and which might... lead to a form of cultural or societal genetic fatalism. Such a seductive belief could create a shift away from preventative medical approaches to health, such as lifestyle or behavioural modifications for certain conditions, to an emphasis on pharmacogenomics 'cures'" (p306 Issa 2002). Some suggest that pharmacogenetic polymorphisms have no influence on drug treatment approximately 50% of the time, due to other factors including environmental interactions (Ingleman-Sundberg 2001); this

highlights the need for further research on the effects of gene-environment interactions on drug response (Issa 2002).

10.2 Confusion between genetic abnormality and genetic variation

'Genetic abnormality' insinuates monogenic properties, such that one gene change results in one phenotype. By contrast, 'genetic variation' implies that the gene change that is being discussed is of a relatively higher prevalence in the population, and can be thought of as a risk-factor (to complex disease, or perhaps to drug response), and that there is not necessarily a direct one-to-one correlation with the presence of a genetic variation to a definitive phenotype. This is because either the gene itself has a mild effect, and/or there are other influencing factors to the phenotype such as gene-gene interactions, or gene-environment interactions.

10.3 Genetic variants associated with ethnic groups

There is speculation on how the matter of race and ethnicity will play into the future of pharmacogenetics. Though the social sciences contend that race is a social construct, and biologists assert that there is more intra-population variation than inter-population variation, medical science has continued to use race and ethnicity as a means of categorizing populations into groups (Genes, drugs and race 2001). This is the case, even though many researchers concede that genes for skin color are very likely not linked to their genes of interest, and that categorizing by race and ethnicity can also take into account environmental and socio-economic differences (McLeod 2001). This could perhaps be a hindrance to the clinical applications of pharmacogenetic research, if race is used as the main identifier in describing populations of different gene frequencies.

Bevan *et al.* (2003) recently held racially diverse focus groups in the south-eastern United States on the topic of pharmacogenetics. They gave their participants the hypothetical option of drugs based on individualized testing, race-based, or non-test based (i.e. uniform prescription). When knowing a prescription was based on racial grouping, many minorities felt that would be harmful to them since membership in a racial category is not always distinguishable. There was also suspicion that drugs for certain races would be damaging for their health because they could be specifically targeted; African-Americans had doubts about the efficacy and safety of drugs marketed for them. Many felt using race in this way was like 'racial profiling' (Bevan *et al.* 2003). Though industry is not aiming to market towards specific ethnic groups, the standard proceedure of preliminary research analyzed by race or ethnicity may have this unintended consequence.

Ultimately, new genetic test technologies have the potential to end the use of possibly stigmatizing racial labels in the clinical setting. However, their current use may be perpetuated by pharmacogenetic studies' collection of such data, and their use as variables in the analysis of the results (Foster *et al.* 2001).

Pharmacogenetic studies may sample from diverse populations to try to represent a broad range of genetic variation (Sankar and Cho 2002). However, if they chose individuals to represent an ethnic or racial group from within communities that are historically stable populations, then they are gathering a small sub-set of variability that is seen in that population, and may not in fact have any bearing on members of the same ethnic or racial group outside of that community (Foster *et al.* 2001).

Previous studies have shown that heart failure in black patients is at a higher rate with a poorer prognosis in comparison to non-black patients. The reason for this outcome is not completely clear; be it due to environmental/diet differences, disparate access to medical care, genetic predisposition, or to pharmacogenetics. This is currently a controversial topic in pharmacogenetic research. Tandem publications in 2001, in the New England Journal of Medicine, highlighted conflicting opinions of race as a factor of drug-efficacy in heart failure trials (Exner *et al.* 2001, Yancy *et al.* 2001). Yancy *et al.* noted no significant interaction between race and treatment of carvedilol. Exner *et al.* stated a differing response to angiotensin-converting enzyme (ACE) inhibitor therapy in black versus white patients with left ventricular dysfunction. Exner *et al.* also noted differing socio-economic and medical histories, factors that were not used in matching the white controls to the black participants. Although the title of the article may suggest otherwise, Exner *et al.* state, "…it must be recognized that racial categorization is only a surrogate marker for genetic or other factors responsible for

individual responses to therapy. Indeed, racial intermixing makes genetic distinctions problematic and any identified difference will certainly not apply to all the members of each stratified group (p1357)."

A firestorm of letters to the editor followed the publication of these articles, including a note stating that some doctors were using the article as a basis for not prescribing ACE-inhibitors to patients who identified as black. It was clarified that the differential in drug response was most likely due to an interplay of polymorphisms within genes for drug receptors, drug-metabolizing enzymes, and/or other factors. More specifically, Exner *et al.* reiterated that the study sought to highlight the need for further research in those arenas; the first step of which was to highlight a population where differentials existed, to provide an impetus to further investigate the reasons for it (Bovet *et al.* 2001).

Interracial and interethnic differences are known in drug metabolizing enzymes. However, it is also known that these differences more often occur in varying frequencies between groups, instead of as unique traits of each group (Wood 2001), such that race and ethnicity alone should be thought of as a risk factor to contribute to the planning of treatment, instead of a definitive answer barring a treatment option. Pharmacogenetics, though in its infancy, should not contribute to the already existent under-serving of minority populations, but should instead augment therapy options.

Some answers may come from a study currently underway. A company called NitroMed is undergoing the first clinical trial for a heart failure medicine ever directed at African-Americans. This is unique in that usually around 80% of clinical trial participants are Caucasian (Holden 2003); thus if there are racial differences to drug response, most drugs are optimized for Caucasians. Follow-up studies are planned to investigate candidate markers for correlations with treatment response (Holden 2003).

In order to increase the likelihood of race and ethnicity not being a discriminating factor in terms of prescribing drugs, a different paradigm may perhaps need to be in place to assist in the future of pharmacogenetic research. An alternative to race-grouping was suggested by Wilson *et al.* (2001). They used a model-based clustering tool to assign individuals to subgroups based on neutral microsatellites within chromosome 1 and the X-chromosome. These results were then compared to the commonly used ethnic labels of their research participants, in regard to the frequency of functionally significant alleles of genes for drug-metabolizing enzymes. They found that clusters derived from polymorphisms alone (without knowledge of ethnicity) were more informative than the broad ethnic labels currently used in research. Wilson *et al.* did not suggest that their tool should be used as a definitive answer to assigning individuals into groups, however they do emphasize that it should be a "priority to assess genetic structure as a routine part of drug evaluation (p 268)."

The consensus of current researchers is that race can be an important identifier in the infancy of pharmacogenetics, such that there would be a difference in population to focus molecular efforts upon; *e.g.*. interracial differences in response to heart failure medications. Please refer to Burchard *et al.* (2003) for a delineation of the importance of race and ethnicity in biomedical research. The goal is to end skin color as a variable and to instead focus on the molecular picture so that in the future there will be good treatment for all. However, the hope is that physicians do not use preliminary findings in their clinic before this goal is met, as even the best data currently available are not enough to justify any race-based generalizations (Holden 2003).

11 The future of pharmacogenetics

11.1 Types of services to be developed

11.1.1 Evaluation of clinical relevance of tests

As previously mentioned, there are currently some examples of pharmacogenetic tests in use, however they are not universally used in clinic. This could be because the clinical utility of all of these tests is not always well established (Pirazzoli and Recchia 2004). "It is frequent that tests are available for use while a lot of questions are still opened with relation to the relevance, utility, applicability, social and ethical impact of the test itself...

Having strong reproduced scientific evidence of a polymorphism influencing response to a drug is essential but not enough for a clinical application" (p359 Pirazzoli and Recchia 2004).

If microarrays are employed for pharmacogenetic testing, "Will every genotypic analyte on the DNA chip represent an equally appropriate use of genetic testing for the patient in question? How will health care providers be able to interpret and counsel so many disparate test results within a practical timeframe? How can all these gene tests be validated and quality controlled to the same degree, or at least to an acceptable level? Clearly our ability to add more and more mutation probes to an array will rapidly outstrip our ability to clinically validate each of them" (p132 Grody 2003).

In general, to assess the usefulness of a pharmacogenetic test, it will be important to have a good reliable estimate of positive and negative predictive values – and these are rarely available in retrospective-study designs (Goldstein *et al.* 2003). Study designs and statistical methods need to be developed that appropriately analyse pharmacogenetics trials. Another high priority is to have standards with which to assess genotype results, and associations, so that false-positive and -negative data will be minimized (Issa 2002).

Given the nature of medicines using pharmacogenetic information, adverse reactions are less likely to be found after the drug has been approved. However, it is for this reason that post-marketing surveillance needs to be all that more vigilant - to make sure this is the case (Shah 2003). As is currently the requirement, Phase IV post-marketing data will also be needed to reassess labeling specifics. Post-approval access to samples and clinical outcome data will be important for the full understanding of pharmacogenetic profiles (Sevilla 2004)

It has been suggested that a regulatory agency be created at the European level to endorse pharmacogenetic tests as they come into practice. Otherwise, it would be difficult for a general practitioner to know which tests to incorporate into their practice, and how to appropriately utilize them. This agency could evaluate clinical utility of the tests in a context dependent fashion, and would state how inclusive the tests could be (given research undertaken in multiple populations, etc.) and the predictive value of such tests; i.e. state which testing is valid, informative and useful in which situations (Sevilla 2004). The Nuffield and Cambridge reports also concluded that establishing benchmarks for clinical validity for both tests and test-drug combinations is a priority, and should be in place for the population for which the drugs/tests are targeted (Melzer *et al.* 2003, Nuffield Council on Bioethics 2003).

11.1.2 Information delivery prior to testing

So far, genetic tests have been primarily used for the diagnosis or prediction of rare, serious monogenic disorders or to identify carriers of a mutation responsible for such disorders. Because these disorders are caused by a single gene mutation, the predictive value of such tests is high and the tests have high relevance not only for the person tested but also for relatives. Therefore, it is generally agreed that in these situations informed consent and genetic counseling be conducted with individuals before they proceed with testing for genetic susceptibility, for carrier testing, or for presymptomatic testing for late-onset disorders (Robertson 2001).

Some feel that most pharmacogenetic tests will not identify disease causing mutations, as their intent is not to determine risk of disease; therefore, they should not necessarily be held to the high level of consent, counseling, and regulation as those for mutational disease testing (Robertson 2001). However, it is not possible to know that the variants will have no connection to disease predisposition in the future, and when a pharmacogenetic test also becomes a test for the disease itself, ethical expectations are raised (Hedgecoe and Martin 2003). Others state that informed consent will still be needed for pharmacogenetic tests, even though they differ from those for monogenic disorders, as they might still "reveal personal information which could be used adversely to a patient's interests" (p209 Moldrup 2001). However, is informed consent truly possible if the patient does not have a true option? Privacy and confidentiality of test results is important for the same reasons. Also, as most individuals have limited knowledge of genetics, autonomy of informed consent in this realm is also limited (Moldrup 2001). It is also suggested that additional safeguards be put in place for those in which consent becomes problematic for research, such as children and incompetent adults (Knoppers *et al.* 2002*)*. Delivery of information prior to pharmacogenetic testing should be assessed on a case specific basis (Sevilla 2004).

Robertson (2001) discusses the following, on the topic that SNP-based testing can still have psychological and/or social implications for the individual. He believes that pre-test conversations by a clinician should include risk/benefits of the test, what the test could uncover, signed informed consent for the DNA sample as well as the genetic test, whether the DNA sample will be stored or discarded, and a discussion of how the privacy of the test results will be handled. If the sample will be stored, they should discuss whether the individual will consent to future tests with the same sample, or if they will be re-consented at the future time. As most information will be the same from patient to patient, much information can be relayed by easily understandable brochures, and supplemented by a quick oral explanation in the doctor's office. Though genetic counseling may not be needed in all cases for pharmacogenetic testing, health care professionals working with these tests should be able to discuss with their patients that they may not qualify for a particular drug, based on their test results, and be able to answer any questions their patients have regarding this issue (Robertson 2001).

Benefits would be that the results of the test could help a physician refine which drugs would best help the individual in treating their disease, and aim to reduce the level of adverse reactions from the drug itself. Risks include that results may indicate that there is no current therapy that matches his/her genetic profile (though some treatment may exist for those of other profiles). This information could also be predictive of his/her risk of developing disease in the future. As many drugs share common metabolic pathways, an individual may be labeled a "non-responder," which could affect his/her self-image, as well as future health care, employment, and/or insurance (Robertson 2001).

11.1.3 Post-test counseling

If genetic test results indicate that an individual is likely to be a poor-responder to a number of common drugs, how will the ordering physician counsel them? This result will have implications for their future medical care.

The Nuffield Council has recommended that test results be directly given to consumers if the results are clear to the medication choice; however complex results are suggested to be relayed through a professional. For those with complex information, additional written information is suggested to be provided to the individual as well (Nuffield Council on Bioethics 2003).

11.1.4 Link between drug prescription and test prescription

One way to reduce the probability of drugs being withdrawn from the market due to adverse reactions (and to curb litigation because of them) is to clearly and accurately put warnings on the label. That way physicians could prescribe medications that would not be contraindicated for their patients due to toxicity predisposition (Shah 2003).

To go even further, requiring a genetic test before prescription would be a stronger stance in minimizing adverse reactions and the physicians' fears of litigation. If testing is tightly linked to prescription, then it again highlights the necessity of physician guidance and education regarding genetics and the use of such tests within pharmacogenetics. Also, if they are linked, financial constraints (due to inability to pay for a potential high cost of genetic test) could limit availability of the test, and could further the divide in the care between those who can afford expensive healthcare, and those who cannot (Shah 2003). Public and private methods of financing healthcare may also influence the uptake and implementation of pharmacogenomics within and between health systems.

11.1.5 Quality assurance

A need for improved quality of labs performing the tests should be underscored (QA/PT very important and should be reinforced). Pharmacogenetic tests are medical tools and should undergo the same rigorous evaluation of quality and clinical utility as other medical diagnostics. Testing laboratories should also interpret results (first level of interpretation, not full consequence of result for patient). Education and training in this field for health care professionals (and other stakeholders) are seen as current deficits, along with education of the public at large (Sevilla 2004).

11.2 Conclusions

11.2.1 Research

There is a deficit of public support as the field is now predominately left to private investment, which is not conducive to setting priorities that are important to the academic world such as pharmacogenetic application to rare diseases. Also, some feel that there needs to be an improvement in the relationship between industry and academia, and increased public-private partnerships. There is a need for not just more research but more coordinated research with more interaction of the academic and industry research teams. There are complaints of lack of awareness of what each other are investigating. Some perceive a tension between the goal of researchers: understanding the genetic cause of variability in drug response, and the goal of industry: overcoming that variability. The paradox in this is that the industry has the blood samples and may not necessarily utilize them, while academia feels they could use them better. It is not necessarily a matter of funding but of linking these separated sectors and increasing collaboration amongst them. Transparency is key in this endeavor, as industry/academic partnerships may breed public distrust. Science as a whole needs to be supported by society (Sevilla 2004).

A specific research need identified by experts, partly due to this lack of academia participation, is more research in genetic epidemiology. A better genotypic characterization of the population is needed, to bring more knowledge on stratification, heterogeneity, ethnicity and genetic diversity. This aspect could currently be improved in pharmacogenetic research being carried out by the pharma industry. Phenotypic knowledge is also lacking. More research in this field should be conducted involving clinicians. A better definition of phenotypes, which is considered essential, can only be done by them. Following this line, notification of adverse drug effects that go through national bodies to EMEA is considered potentially invaluable information for pharmacogenetic research and academia believes it should also be made available to them to assist in their research endeavors. There should also be more research to develop mathematical tools and models for complex traits association studies (Sevilla 2004).

11.2.2 Education/engagement

Additionally, more research on the public perception of pharmacogenetics needs to be undertaken; such research at this stage may prevent some of the problems that occur when the public is confronted with new technology. Finally, research into additional communication skills for health care providers (delivering probabilistic genetic information to the patient in the right way) still needs to be enhanced. Many health professionals have problems making sense of probabilistic information. As they will need to interpret test results and communicate them to patients, education for these professionals will be crucial (Sevilla 2004).

11.2.3 Regulatory

Clinical utility of pharmacogenetic tests should be proven before any commercialization takes place. A European platform linked to, but independent from, EMEA was suggested by experts to carry out this evaluation. Health Technology Assessment, linked to clinical utility, should be reinforced. Drugs already approved and in the market might have to be re-evaluated – but if so, how would newly found information be disseminated to physicians? There is also a perceived conflict between existing orphan drug regulation and the possibility that pharmacogenetics strategies will create new orphan diseases; this will need to be resolved through policy and legislation. The current stringent regulatory frame of drug development decreases the already difficult interaction between academia/industry in pharmacogenetic research – an interaction that both sides would like to see grow stronger. Issues of potential discrimination, public perception, data privacy/sample handling, and transparency, also need to be discussed further (Sevilla 2004).

11.2.4 Standard of practices

Since pharmacogenetics is currently evolving, not much is known about the long-term effects of pharmacogenetic-based treatments. If this system allows drugs to be on the market which will be quite toxic to some individuals, but beneficial to others, what are the implications if pre-genotyping is overlooked before prescribing? (Moldrup 2001).

As previously mentioned, after the results have been received, the physician, or even the patient, may still request that a drug be prescribed, even though there may be a high risk of adverse effects or poor efficacy. How will this "off-label" use be handled? Will drug benefit plans pay for this? (Robertson 2001) Because pharmacogenetics will likely represent probabilistic rather than definitive information, it is suggested that there be some prescriptive flexibility allowed (i.e. not letting the test solely dictate the treatment), as patients may react to a drug in a manner not predicted by their genotype. As we know, there is a complex interplay that occurs in the way each person reacts to a particular drug. Given this fact, physicians should still be allowed to use their professional experience and expertise when prescribing medication for their patients (Shah 2003), and use appropriate clinical monitoring in order to detect harmful side effects (Sevilla 2004).

11.2.5 Ethical issues

Though data gathering of ethnicity in research may be helpful in the onset (to help explain variability), discrimination based on race or ethnicity should be avoided. Also, the needs for the subsequently labeled "non-responder" group should be taken into consideration, especially if no other therapy is available. [It should be reiterated that there should be no such labeling as 'non-responder' as pharmacogenetics will most likely not reveal absolutes, but instead likelihoods.] Additional ELSI research is also needed to take place alongside the other research elements (such as issues of regulation, and public engagement work), as ethical considerations are fundamental to these areas and should be treated as such, rather than as a separate area of research (Sevilla 2004).

11.3 Final thoughts

Research should continue in the pursuit to better understand polymorphic variation in the genes that encode the functions of metabolic enzymes, transporters, receptors, and other proteins in relation with drugs and other chemical compounds introduced in the human metabolism. Pharmacogenetics has so far been overestimated in its clinical application, and initial expectations have not yet been fulfilled. It is still in a very preliminary stage (research phase) with as yet a paucity of vigorous studies proving clinical validity and utility of research output. Given the current state of research, and industry patterns that are currently evident, it does not seem as though pharmacogenetics will affect every individual's medical care, or every medicine prescribed, as some have suggested. It is also important that on-going research not be underestimated as a counter-reaction. The potential, though not consummated, is still there. Genetic epidemiology and molecular biology research efforts should continue – in a more robust fashion including prospective studies – so that clinical validity and utility are endpoint goals and benefits to the greater public health are realized.

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Appendix 1: INTERNATIONAL AND NATIONAL FRAMEWORKS ON PHARMACOGENETICS

I- European Organizations

- *European Agency for the Evaluation of Medicinal Products, Report to the CPMP on the EMEA seminar on the use of pharmacogenetics in the drug development process, EMEA, London, 2000 (EMEA/CPMP/1483/00)*
No guidelines are proposed in this document, however the need is noted for a harmonized approach in pharmacogenetic trial protocols, as well as a harmonized genetic terminology for this usage.

- *European Agency for the Evaluation of Medicinal Products, Position paper on terminology in pharmacogenetics, EMEA, London, 2002 (EMEA/CPMP/3070/01)*
This document was published in the goal of harmonizing the definitions of the terms pharmacogenetics and pharmacogenomics, as well as the terms used in the handling of samples and data for pharmacogenetic testing.

- *European Agency for the Evaluation of Medicinal Products, Concept paper on pharmacogenetics, EMEA, London, 2003 (CPMP/4445/03)*
An ad hoc Pharmacogenetics working group has been established, that will monitor the technical progress and provide input into the field for technical discussions and preparations of guidance documents.

-*The Pharmacogenetics Working Group (www.pharmacogeneticsworkinggroup.org)*
This group is composed of pharmaceutical companies involved in clinical drug trials and genotyping, whose goal is to promote the understanding and development of pharmacogenetics by addressing non-competitive regulatory, legal, and ethical issues.
They have published the following articles:
*Terminology for sample collection in clinical genetic studies, Pharmacogenomics J, 1, 2001: 101-103.
*DC Anderson *et al.,* Elements of informed consent for pharmacogenetic research; perspective of the pharmacogenetics working group, Pharmacogenomics J, 2, 2002: 284-292.

The following are EU directives that will be/are affecting pharmacogenetics:

-*The European Union Data Protection Directive (95/46/EC) 1995,* (*Official Journal L 281, 23/11/1995 p. 31 - 50*)
This directive delineates principles relating to data quality (section I), criteria for making data processing legitimate (section II), information to be given to the data subject (section IV), data subjects right of access to data (section V), data subject's right to object (section VII), and confidentiality and security of processing (section VIII). Pharmacogenetic data is a subset of medical data, and therefore would be affected by this directive.

-*The European Union In Vitro Diagnostic Device Directive (98/79/EC) 1998, (Official Journal L 331, 7/12/1998 p. 1 - 37)*
Compliance with this directive has been required since December 2003. It is currently up for debate how much this new directive will affect the genetic testing related to pharmacogenetics, as such a test has yet to go through the system. In theory, it should be as per any other test, but time will tell. It is still unknown how the test approval will be coordinated with the drug approval as each goes to a separate responsible body. Not all pharmacogenetic testing will be covered under this directive, as some will be done in a research setting while others are being considered/worked up.

-*The European Union Clinical Trial Directive (2001/20/EC) 2001, (*Official Journal L 121, 1/05/2001 p. 34 - 44*)*

This directive covers clinical research in the EU and is due to be transposed in member states by May 2004. All medical research meeting the directive criteria will similarly apply to pharmacogenetics.

-European Commission, Detailed guidance on the application format and documentation to be submitted in an application for an ethics committee opinion on the clinical trial on medicinal products for human use, (ENTR/F2/BL D(2003)
This guidance document references pharmacogenetics on page 23, and states: "In clinical trials where genetic testing is included, this should be clearly explained to the subject. The information should give the background and purpose of the genetic tests, the planned anlayses and whether the samples will be kept to make future analyses possible in conjunction with the planned project. When applicable, the information on the genetic part of the trial might be separate from the information on the other part. Information should be provided on the possibility for the subject to abstain from the genetic testing but still be able to participate in the non-genetic part of the trial, according to national recommendations."

II- European Countries

Belgium

-Comité Consultatif de Bioéthique, Avis no. 26 du 15 décembre 2003 concernant l'introduction d'un volet pharmacogénétique dans les protocoles expérimentaux
This document includes recommendations for local ethics committees, investigators, and authorities who work with pharmacogenetic research. Topics include multiple issues such as patient autonomy, consent, confidentiality, and sample anonymization.

Italy

-Italian Society of Human Genetics, Proposta di lineeguida per la valutazione di una sperimentazione farmacogenetica/ Italian proposed guidelines for the evaluation of pharmacogenetic research, 2002 (http://sigu.univr.it/sigu/html/documenti/index.shtml)
These guidelines were composed as a tool for those who prepare as well as evaluate pharmacogenetic protocols. They present some operating guidelines, though are not intended to be a fixed set of principles, but instead the beginning stage of an evolving process of understanding the science and its implications.

III- United States of America

-United States Food and Drug Administration/ Center for Drug Evaluation and Research/ Center for Biologics Evaluation and Research, Guidance for Industry Pharmacogenomic Data Submissions, Draft guidance, 2003 (\\CDS029\CDERGUID\5900dft2.doc 10/29/03)
(located at: http://www.fda.gov/cder/guidance/5900dft.pdf)
The draft of these non-binding recommendations was published in November 2003. The final version of this guidance document will be available after February 2004. "This draft guidance is intended to facilitate scientific progress in the field of pharmacogenomics and to facilitate the use of pharmacogenomic data in informing regulatory decisions. It discusses when pharmacogenomic data is to be submitted, the format of that data, and how the data will be used. Pharmacogenomic data must be submitted to an IND [investigational new drug applications] if any of the following apply: (1) the test results will be used for decision making in any clinical trial, or in an animal trial used to support safety; (2) the sponsor is using the test results to support scientific arguments pertaining to, for example, the safety, effectiveness, dosing and pharmacology of the drug; or (3) the test results constitute a known valid biomarker for physiologic, pathophysiologic, pharmacologic, toxicologic, or clinical states or outcomes in humans, or is a known valid biomarker for a safety outcome in animal studies. Data submission for NDAs [new drug applications] is required if it is used to support scientific/clinical arguments or for labeling purposes. Otherwise, data submission is voluntary."

-*The Pharmacogenetics Research Network*
(http://www.nigms.nih.gov/pharmacogenetics/research_network.html)
Sponsored by the National Institute of General Medical Sciences, and began from a 1998 recommendation by an NIGMS Pharmacogenetics working group

-*Consortium on Pharmacogenetics, Pharmacogenetics: Ethical and Regulatory Issues in Research and Clinical Practice, 2002*
The consortium is composed of bioethicists, public policy experts, and individuals from biotechnology and pharmaceutical industries. This publication was published to contribute to their goal of providing "a model for extensive, sustained collaborative efforts between industry and academia on a wide range of public policy issues in the pharmaceutical and biotechnology industries."

Appendix 2: INTERNATIONAL AND NATIONAL REGULATORY FRAMEWORKS

Adapted from a previous PPPC document entitled:
PROVISION OF GENETIC SERVICES IN EUROPE - CURRENT PRACTICES AND ISSUES

As pharmacogenetics is a relatively new area in the legal/regulatory arena, there are not many guidelines exclusively made for this field. In lieu of that, we have included European frameworks for genetic testing in general. Much of the following is relevant for future applications of genetic testing for complex disease as well as for pharmacogenetics.

I- International Organizations

- World Health Organization, Report on Community approaches to the control of hereditary diseases, Geneva, WHO, 1985
This report is concerned with the community aspects of genetics services. It seeks to illustrate their relevance for health care by addressing some quantifiable examples of the control of hereditary diseases; important new technical developments; approaches that may be incorporated into primary health care; evaluation of community-based services; gaps in the existing medical structure that need to be corrected in order to deliver these services; the importance of genetic information in health education; the ethical problems associated with genetics services; and research needs and opportunities.

- World Medical Association Statement on Genetic Counseling and Genetic Engineering, 1987 (http://www.wma.net/e/policy/17-s-_e.html)
The World Medical Association adopted this statement to assist physicians with the ethical and professional issues that raised from scientific advances in the field of genetics.

- World Health Organization, Community Genetic services in Europe, Geneva, WHO, 1991
This report gives countries the necessary information to start the rational planning of genetic services based on the assessment of needs.

- World Medical Association Declaration of the Human Genome Project, 1992 (http://www.wma.net/e/policy/17-s-1_e.html)
The World Medical Association recommends that "The genetic service should be easily accessible to everyone in order to prevent its exploitation by only those who have resources which will increase social inequality. There is a need for international information and transfer of technology and knowledge between countries".

- World Health Organization, A Declaration on the Promotion of Patients' Rights in Europe, Geneva, WHO, 1994 (http://www.fgov.be/WHI3/per…onths/wwhv2n1tekst/WWH19019804.htm)
This document sets a series of principles for the promotion and implementation of patients' rights in WHO's European Member States. Under the first principle, "Human rights and values in health care", it is stated that "**everyone has the right to the protection of health as is afforded by appropriate measures for disease prevention and health care, and to the opportunity to pursue his or her own highest attainable level of health**" (Principle 1.6). The second principle on "Information" stipulates that "information about health services and how best to use them is to be made available to the public in order to benefit all those concerned" (Principle 2.1). The fifth principle regarding "Care and treatment" establishes that "everyone has the right to receive health care as is appropriate to his or her health need, including preventive care and activities aimed at health promotion. Services should be continuously available and accessible to all equitably, without discrimination and according to the financial, human and material resources which can be made available in a given society" (Principle 5.1). According to Principle 5.2, "patients have a collective right to some form of representation at each level of the health care system in matters pertaining to the planning and evaluation of services, including

the range, quality and functioning of the care provided". Finally, "patients have the right to a quality of care which is marked both by high technical standards and by a humane relationship between the patient and health care providers" (Principle 5.3).

- *World Medical Association Declaration of the Rights of the Patient, 1995 (http://www.wma.net/e/policy/17-h_e.html)*
The World Medical Association considers that physicians and other persons or bodies involved in the provision of health care have a joint responsibility to recognize and uphold the principal rights of the patient. In the context of biomedical research, the human subject is entitled to the same rights and consideration as any patient in a normal therapeutic situation. Consequently, in regard to the "Right to medical care of good quality", The Association recommends that "Every person is entitled without discrimination to appropriate medical care. (…) Quality assurance always should be a part of health care. Physicians, in particular, should accept responsibility for being guardians of the quality of medical services" (Principles 1a-1d). Principle 9 on "Right to Health Education" states that "Every person has the right to health education that will assist him/her in making informed choices about personal health and about available health services. The education should include information about healthy lifestyles and about methods of prevention and early detection of illnesses. The personal responsibility of everybody for his/her own health should be stressed. Physicians have an obligation to participate actively in educational efforts".

- *World Health Organization, Control of Hereditary Diseases, Technical Report Series Nº 865, Geneva, WHO, 1996*
This report offers advice on the organization of genetic services in industrialized and developing countries alike, and discusses the ethical, social and legal aspects of genetic technology in medicine, concluding that the broadest ethical issue in the area of genetic services is their limited availability.

- *World Health Organization Proposed International Guidelines on Ethical Issues in Medical Genetics and the Provision of Genetic Services, Geneva: WHO, 1997 (http://wwwlive.who.ch/ncd/hgn/hgnethic.htm)*
The proposed guidelines are designed to assist decision-makers at both national and international levels to protect people and families with genetic disabilities, to recognize the great potential of advances in human and medical genetics for public health, and to develop policies and practices that will ensure that these applications can become accessible to all and are provided with due regard to ethics and justice worldwide.

The issues related to ethics and the provision of medical genetic services are the following:
1) General ethical considerations: "The medical application of genetic knowledge must be carried out with due regard to the general principles of medical ethics".
2) The proper use of genetic data: **"It is ethically imperative that genetic data should only be used to the advantage of members of a family or ethnic group, and never to stigmatize or discriminate against them".**
3) Voluntary use of genetic screening and testing: **"Every genetic test shall be offered in such a way that individuals and families are free to refuse or accept according to their wishes and moral beliefs. All testing should be preceded by adequate information about the purpose and possible outcomes of the test and potential choices that may arise.** Children shall only be tested when it is for the purpose of better medical care, as in the case of newborn screening when early treatment will be of benefit to the child".
4) Prenatal testing: "Prenatal diagnosis should be offered to those who need it, but there must be no pressure on couples to accept such testing, nor to use the results of the test to compel either continuing or terminating a pregnancy when the fetus is affected with a genetic disorder. (…) Prenatal diagnosis should be done only to give parents and physicians information about the health of the fetus".
5) Justice demands equitable access to services: **"Genetic services for the prevention, diagnosis and treatment of disease should be available to all, without regard to ability to pay, and should be provided first to those whose needs are greatest".**
6) **"Genetic data should be treated as confidential at all times".**
7) Genetic counseling: **"Counseling is essential before any genetic testing is carried out, and should continue afterwards if the results entail choices for the person and family tested. Genetic counseling should be available to all, and should be as non-directive as possible".**

8) **"Education about genetics for the public and health care professionals is of paramount importance.** (…) It is important that education about genetic principles relevant to human health be emphasized appropriately for all people in all cultures. Education is a two-way process, and geneticists and other health care professionals have much to learn from support and advocacy groups representing those with genetic disorders. Such groups are an integral part of genetic services, and should be guaranteed a voice in policy and education".

- *United Nations Educational, Scientific and Cultural Organization, The Universal Declaration on the Human Genome and Human Rights, 1997 (http://www.unesco.org/ibc/uk/genome/project/index.html)*
The UNESCO Declaration is the first international normative instrument in the field of bioethics. Article 5 states that " a) Research, treatment or diagnosis affecting an individual's genome shall be undertaken only after rigorous and prior assessment of the potential risks and benefits pertaining thereto and in accordance with any other requirement of national law".

- *World Health Organization, Medical Genetic Services in Latin America, Report of a WHO Collaborating Center for Community Genetics and Education, 1998 (http://whqlibdoc.who.int/hq/1998/WHO_HGN_CONS_MGS_98.4.pdf)*
This document is not a formal publication of the WHO. In the framework of the 9th International Congress of Human Genetics in 1996, a group of experts in medical genetics from Latin America discussed the situation of medical genetics in the Region and set forth a series of recommendations for the continuing development of the field in the areas of services, training and research.

- *World Health Organization/WAOPBD, Services for the Prevention and Management of genetic Disorders and Birth Defects in Developing Countries, Report of a joint WHO/WAOPBD meeting, The Hague, January 1999 (http://www.who.int/ncd/hgn/reppub_malta.htm)*
This document is not a formal publication of the WHO. An Advisory Group constituted mostly by geneticists from 13 developing countries was convened on January 5-7, 1999 by the World Health Organization and the World Alliance of Organizations for the Prevention of Birth Defects, to address the lack of genetic services in the developing world and make recommendations for their growth. Its main recommendations are: need that health professionals and public health officials of developing countries recognize the burden imposed by birth defects and genetic disorders; need for political will and commitment for their prevention and management; define goals of genetic services in terms of individual and family well-being as well as of public health; improve reproductive health, prenatal and newborn care with particular attention to maternal age, nutrition and teratogen avoidance; organize comprehensive genetic services integrated with other relevant health services, rooted in the primary care level, with proper referral channels to existing genetic centers; prioritize prevention programs and services according to prevalence, severity and predicted outcomes of interventions; train health professionals in genetics; educate the public in genetics; encourage the formation and support of parent/patient organizations; and respect ethical principles and cultural diversity.

- *World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, 2000 (http://www.wma.net/e/policy/17-c_e.html)*
The World Medical Association Declaration of Helsinki was originally adopted by the 18th World Medical Assembly in 1964 and has subsequently been revised (1975, 1983, 1989, 1996, 2000). The Declaration provides ethical guidance to physicians and other participants in (bio)medical research involving human subjects. "It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty" (Principle 2).

When medical research is combined with medical care, additional standards apply to protect the patients: "in the treatment of a patient, when proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving-life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy" (Principle 32).

- Organization for Economic Co-operation and Development, GENETIC TESTING Policy Issues for the New Millennium, Paris, OECD, 2000

An OECD workshop on genetic testing held in Vienna on 23-25 February 2000 was devoted to the discussion of ways to optimize health care benefits while protecting individuals and their families from the potential of discrimination on the basis of the testing. Participants identified four areas where co-ordinate international action is urgently needed: 1) Development of internationally recognized and mutually compatible best practice policies for quality assurance and accreditation of genetic tests and services; 2) Development of compatible electronic information systems in genetics; 3) Enhancement of current counseling services, genetic training and public information; and 4) Examination of possible impacts of monopolistic licensing practices.

- Council for International Organizations of Medical Sciences: Revision of the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Geneva, 2002
*(*http://www.cioms.ch/frame_guidelines_nov_2002.htm*)*

"The Guidelines relate mainly to ethical justification and scientific validity of research; ethical review; informed consent; vulnerability of individuals, groups, communities and populations; women as research subjects; equity regarding burdens and benefits; choice of control in clinical trials; confidentiality; compensation for injury; strengthening of national or local capacity for ethical review; and obligations of sponsors to provide health-care services."

- World Health Organization, Collaboration in Medical Genetics, Report of a WHO meeting, Toronto, April 2002 (http://www.who.int/ncd/hgn/publications.htm)

Experts recommendations made for WHO included the following :

- To develop and strengthen comprehensive medical genetic services linked to primary health care as the key strategy for the prevention and control of conditions with genetic causation that include genetic counseling, the appropriate use of safe and effective technologies, and the support to parent/patient organizations.
- To assist Member states in establishing undergraduate and postgraduate education programs for the teaching of medical genetics for all health professions (physicians, nurses, psychologists, public health professionals, etc) ; in developing training modules on genetic counseling and application of genetics/genomics technologies in clinical practice ; and in improving awareness of genetics among policy makers, community leaders, patient/parent organizations, journalists and the general public.
- To assist Member states in assembling regional expert interdisciplinary advisory groups to recommend practical regulatory systems which will ensure the safety and effectiveness of medical applications of new genetic/genomic technologies before they are introduced on the market.

- United Nations Educational, Scientific and Cultural Organization, The International Declaration on Human Genetic Data, 2003 (http://www.unesco.org/confgen/2003/genetic)

'With the Declaration, human genetic data now have their own standard-setting instrument, laying down the ethical principles that should govern their collection, processing, storage and use.'

II- European Institutions

- European Union, Council Directive 93/16/EEC of 5 April 1993 to Facilitate the Free Movement of Doctors and the Mutual Recognition of their Diplomas, Certificates and other Evidence of Formal Qualifications (http://www.ilo.org/public/english/employment/skills/recomm/instr/eu_5.htm)

The EU directive facilitates the free movement of doctors and the mutual recognition of their diplomas, certificates and other evidence of formal qualifications. Article 4 states that each Member State will recognize the formal qualifications in specialized medicine awarded to nationals of Member States by the competent authorities or bodies of other Member States. Article 6 states that some countries award qualifications in a specialized branch of medicine which has been formally constituted by national regulations in that country, but that the branch of medicine may not be formally recognized for all Member States. Article 24 lays down minimum requirements for training leading to a formal qualification in specialized medicine.

- The Group of Advisers on the Ethical Implications of Biotechnology to the European Commission, Opinion N° 6 on Ethical Aspects of Prenatal Diagnosis, 1996

The Group of Advisers to the European Commission on the Ethical Implications of Biotechnology considers that "the offer and use of prenatal diagnosis presuppose good quality social and medical services, especially adequately trained staff, suitable equipment and reliability of the techniques. Safeguards against unethical or unprofessional practices must be in place for all centers offering these procedures. These centers must be officially recognized. Because the consequences of the information can be of the greatest importance to all concerned, it is an ethical imperative that counseling, which requires a specific competence, should be of good quality and widely available. This implies that there must be sufficient trained medical, nursing and other professionals to provide one-to-one counseling when prenatal diagnosis is performed. In accordance with the subsidiary principle, the European Union should stir to achieve a high and comparable level of quality of the training of the professionals, namely concerning the genetic counseling, and of the services provided in different Member States".

- *Council of Europe, Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine, 1997 (http://www.coe.fr/fr/txtjur/164fr.htm)*
The Council of Europe is at the origin of the first international convention in the field of bioethics. The Convention is the first internationally binding legal text designed to protect people against the misuse of biological and medical advances. This text has legal effect in the Council of Europe's member States that have ratified it. The Committee of Ministers of the Council of Europe has also taken the issues of predictive medicine in a series of recommendations.

The Convention sets out to preserve human dignity, rights and freedoms, through a series of principles and prohibitions. According to Article 5, **a genetic test "may only be carried out after the person concerned has given free and informed consent to it";** Article 12 states that "tests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counseling". The restriction of genetic diagnostics to health or scientific purposes is reinforced by Article 11, which states that "any form of discrimination against a person on grounds of his or her genetic heritage is prohibited". Article 13 forbids germ-line therapy. An additional protocol on the prohibition of human cloning was added in January 1998.

- *The Committee of Ministers of the Council of Europe: Recommendations*
Before the member States of the Council of Europe, the other States and the European Community signed the Convention for Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine, the Committee of Ministers of the Council of Europe took the issues of medical genetics under consideration in a series of Four recommendations:
- Recommendation N° R (90) 3 on prenatal genetic screening, prenatal genetic diagnosis and associated genetic counseling
- Recommendation N° R (92) 3 on genetic testing and screening for health-care purposes
- Recommendation N° R (94) 11 on screening as a tool of preventive medicine
- Recommendation N° R (97) 5 on the Protection of Medical Data

The principles contained in these recommendations governed 1) the rules for good practice (informing the public, quality of genetic services, criteria for selecting diseases suitable for testing, counseling, economic aspects, quality assurance), 2) access to genetic tests (equality, self-determination, non compulsory nature of tests, non discrimination, privacy), 3) data protection and professional secrecy (data protection, professional secrecy, separate storage of genetic information, unexpected findings), and 4) research (supervision, handling of data).

- *Council of Europe, Recommendation N° R (92) 3 on genetic testing and screening for health-care purposes, 1992 (http://www.coe.fr/cm/ta/rec/1992/92r3.htm)*
Governments of Member States are recommended to be guided in their legislation and policy by a series of 13 recommendations to ensure respect for certain principles in the field of genetic testing and screening for health care purposes, including medical research.

Principle 1, "Informing the public", states that "a) **Plans for the introduction of genetic testing and screening should be brought to the notice of individuals, families and the public; b) The public should be informed about genetic testing and screening, in particular their availability, purpose and implications - medical, legal, social and ethical - as well as the centers where they are carried out. Such information should start within the school system and be continued by the media".**

Principle 2, "Quality of genetic services" states that: "a) **Proper education should be provided regarding human genetics and genetic disorders, particularly for health professionals and the paramedical professions, but also for any other profession concerned. b) Genetic tests may only be carried out under the responsibility of a duly qualified physician. c) It is desirable for centers where laboratory tests are performed to be approved by the State or by a competent authority in the State, and to participate in an external quality assurance".**

Principle 3, "Counseling and support" stipulates that "a) **Any genetic testing and screening procedure should be accompanied by appropriate counseling, both before and after the procedure. Such counseling must be non-directive. The information to be given (…) must be adapted to the circumstances in which individuals and families receive genetic information".**

Principle 4, "Equality of access - non discrimination" states that: "a) **there should be equality of access to genetic testing, without financial considerations and without preconditions concerning eventual personal choices. b) No condition should be attached to the acceptance or the undergoing of genetic tests.** c) The sale to the public of tests for diagnosing genetic diseases or a predisposition for such diseases, or for the identification of carriers of such diseases, should only be allowed subject to strict licensing conditions laid down by national legislation".

Principle 5, "Self-determination" states that: "a) the provision of genetic services should be based on respect for the principle of self-determination of the persons concerned. For this reason, **any genetic testing, even when offered systematically, should be subject to their express, free and informed consent".**

- *Council of Europe, Recommendation N° R (94) 11 on Screening as a Tool of Preventive Medicine, 1994 (http://www.coe.fr/cm/ta/rec/1994/94r11.htm)*
Governments of Member States are recommended to take account in their national health planning regulations and legislation of the conclusions and recommendations set out in the appendix of this recommendation. "Because there are differences in health needs and health services, as well as in ethical values and in legal norms and rules between countries, the decision to implement a particular screening program should be taken in cooperation with the medical profession by each country" (Principle 1.7). The organization of a screening program must be tailored to the structures of the preventive and curative systems. **"If appropriate structures in the curative health care system are lacking, screening should not be implemented until they are developed"** (Principle 6.3).

- *Council of Europe, Recommendation N° R (97) 5 on the Protection of Medical Data, 1997 (http://www.coe.fr/dataprotection/rec/r(97)5eexp.htm)*
Under Chapter 4 on "Collection and processing of medical data", "medical data [which includes genetic data] may be collected and processed if permitted by law for preventive medical purposes or for diagnostic or for therapeutic purposes with regard to the data subject or a relative in the genetic line, or to safeguard the vital interests of a data subject or of a third person" (Principle 4.3). Principle 4.4 states that "if medical data have been collected for preventive medical purposes or for diagnostic or therapeutic purposes with regard to the data subject or a relative in the genetic line, they may also be processed for the management of a medical service operating in the interest of the patient, in cases where the management is provided by the health-care professional who collected the data, or where the data are communicated in accordance with principles 7.2 and 7.3 [on the conditions of communication]". Regarding genetic data, "the collection and processing of genetic data should, in principle, only be permitted for health reasons and in particular to avoid any serious prejudice to

the health of the data subject or third parties. However, the collection and processing of genetic data in order to predict illness may be allowed for in cases of overriding interest and subject to appropriate safeguards defined by law" (Principle 4.9).

- Organisation for Economic Cooperation and Development, Genetic Testing: Policy Issues for the New Millennium, 2000 (http://www1.oecd.org/dsti/sti/s_t/biotech/act/gentest.pdf)
In February 2000, the Organization for Economic co-operation and Development (OECD) held a workshop on "Genetic Testing: Policy Issues for the New Millennium" in Vienna. The principal goal of the workshop was to consider whether the various approaches of OECD Member countries for dealing with new genetic tests are appropriate and mutually compatible. Participants identified a number of policy areas requiring international coordination and the establishment of coherent international policies.

- *European Union, Charter of Fundamental Rights of the European Union, 2000*
Article 35 on "Health care" of the Charter states that "Everyone has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices. A high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities".

- *European Parliament, Temporary Committee on Human Genetics and Other New Technologies in Modern Medicine, Report on the ethical, legal, economic and social implications of human genetics, 2001 (http://www.europarl.eu.int/comparl/tempcom/genetics/rapfin/rapfin_en.doc)*

On 13 December 2000 the European Parliament decided to set up a temporary committee on human genetics and other new technologies in modern medicine, which was to remain in existence for one year. According to the brief conferred on it, the committee had the tasks of:

- compiling as complete an inventory as possible of new and potential developments in human genetics and of their uses, so as to provide Parliament with a detailed analysis of such developments necessary to enable it to assume its political responsibilities;

- examining the ethical, legal, economic and social problems posed by such new and potential developments and by their uses;

-examining and recommending to what extent the public interest requires a proactive response to such developments and uses;

- providing an orientation for Parliament and the other Community institutions with regard to research in human genetics and other new technologies in

- *Council of Europe, Recommendation 1512: Protection of the Human Genome, 2001 (http://star.coe.fr/ta/TA01/EREC1512.htm)*
The Council of Europe's Parliamentary Assembly notes that the human genome international research project, in view of the numerous and unimaginable consequences that it might have for medicine, conjures up scenarios for all humanity that raise numerous ethical questions, while holding out the promise of enormous improvements in the quality of life. The genetic age will dawn with the completion of the project: diagnosis will become objective, and it will be possible to identify the presence of genetic disorders or a genetic predisposition to illnesses at an early stage. In many cases, gene therapy will become possible, and this will basically give rise to a form of genetic engineering designed. At the same time, the Assembly is aware of the enormous ethical implications of further research on the human genome, including some of a negative nature. These include questions regarding the cloning of cells, the conditions ruling genetic testing and the divulging and use of obtained information. The Assembly calls, *inter alia,* through the establishment of a Euroforum on Human Genetics, for the widest possible participation by citizens in the discussion on the human genome through the involvement of the European media and suitable and accurate information by the Council of Europe.

- *European Society of Human Genetics, Proposed statement on Formal recognition of medical genetics as a medical specialty in Europe, June 2001 (http://www.eshg.org)*

The European Society of Human Genetics recommends a *Formal recognition of medical genetics as a medical specialty in Europe* in order "to aid the provision and development of genetic services for individuals and families in Europe". (…) "The ESHG believes that there are many advantages for the specialty to be recognized internationally, in particular to enable the full impact of the Human Genome Project to be translated into practice across all specialties". (…) "The ESHG believes that the benefits of recognizing medical genetics as a specialty will include (1) the establishment and implementation of training programmes; (2) the identification of resources required for service and training; (3) recruitment to the specialty in its own right; (4) the development of relationships between medical geneticists and other specialties; and (5) the dissemination of information to and training for non genetics health professionals".

-European Commission, Communication from the Commission to the council, the European parliament, the Economic and social committee, and the Committee of the regions; Life sciences and biotechnology: A strategy for Europe, Brussels, 2002 (http://europe.eu.int/eur-lex/en/com/cnc/2002/com2002_0027en01.pdf)
"The commission proposes a strategy to respond with responsible, science-based and people-centred policies on an ethical basis. This strategy aims to allow Europe to benefit from the positive potential of life sciences and biotechnology, to ensure proper governance, and to meet Europe's global responsibilities."

- European Commission Joint Research Centre, Institute for Prospective Technological Studies; Towards quality assurance and harmonisation of genetic testing services in the EU, 2003 (EUR 20977 EN) (located at: http://www.jrc.es/home/publications/publication.cfm?pub=1124)
"The report reviews the dimension of genetic testing in the EU, in terms of active laboratories, conditions tested and numbers of tests. It then moves to describe the situation of quality assurance of these services, analyzing the potential weaknesses of existing networks and schemes for quality assurance (QA): the low participation of laboratories, the actual costs of QA schemes, the coverage of rare diseases, the lack of certified reference materials and the ambiguities in the interpretation of certain regulations. It finally presents a foresight exercise with scenarios for the future of genetic testing services in Europe. As a conclusion, several lines of action are suggested in the study in order to diminish current and potential weaknesses of QA of genetic testing services."

- Council of Europe Steering Committee on Bioethics (CDBI), Draft additional protocol to the convention on human rights and biomedicine, on biomedical research, (CDBI/INF (2003) 6 rev), Strasbourg, 2003 (http://www.coe.int/T/E/Legal_Affairs/Legal_co-operation/Bioethics/Activities/Biomedical_research/CDBI-INF(2003)6eREV.pdfm)
This protocol "covers the full range of research activities in the health field involving interventions on human beings" and specifically applies only to *in vivo* and not *in vitro* research. Article 3 states that "the interests and welfare of the human being participating in research shall prevail over the sole interest of society or science." Chapter III discusses ethics committees, chapter IV: information and consent, chapter V: protection of persons not able to consent to research, chapter VI: specific situations, chapter VII: safety and supervision, chapter VIII: confidentiality and right to information. The appendix includes information to be given to ethics committees.

- European Commission, Ethical, legal and social aspects of genetic testing:research, development, and clinical applications, Brussels, 2004
(http://europa.eu.int/comm/research/conferences/2004/genetic/report_en.htm)

-European Commission, 25 Recommendations on the ethical, legal and social implications of genetic testing, Brussels, 2004
(http://europa.eu.int/comm/research/conferences/2004/genetic/recommendations_en.htm)

- European Union Data Protection Working Party, Article 29, Working document on genetic data, 12178/03/EN WP91, Brussels, 2004
(http://europa.eu.int/comm/internal_market/privacy/docs/wpdocs/2004/wp91_en.pdf)
This document identifies areas of concern relating to the processing of genetic data and to contribute to a more harmonised approach in the light of the national measures adopted by EU Member States under the Data Protection Directive (95/46/EC).

III- European Countries

The provision of genetic services is not specifically legislated in most European countries. Genetic testing legislation has been implemented in Austria, Belgium, France, Norway, Sweden, Switzerland, and the Netherlands. Denmark, Germany and the United Kingdom have issued policy statements or recommendations on the application of genetic testing. There are recommendations concerning genetic services provided by different actors including human genetics societies and societies of clinical geneticists in many countries. In the following the laws and also the less formal recommendations whenever known to us are presented for each country.

Austria

- The Gene Technology Act (Law BGB 510/1994), 1994 (http://www.gentechnik.gv.at/gentechnik/B1_orientierung/gen_10084.html)
The "Gene Technology Act" regulates genetic testing. Gene analysis, as it is defined in this Act, comprises molecular biological investigations for the identification of disease-causing mutations. Such examinations are allowed only for research or medical purposes. According to this act, laboratories where genetic tests for the diagnosis of a predisposition or for the identification of a carrier status of inherited diseases are performed have to be accredited by the competent authority. Genetic tests for the diagnosis of manifested diseases do not require an authorization but are subject to strict measures for data protection.

To carry out predictive genetic testing, laboratories have to meet a number of specific requirements. These include quality of the technical equipment, adequate qualification and experience of the performing staff, appropriate confidentiality measures. Genetic counseling has to be carried out before and after genetic testing, and has to include psychological and social considerations as well. The patient has to provide written informed consent prior to the performance of a predictive genetic test.

In addition to the Gene Technology Act, on 23 January 1998, the Austrian Advisory Board on Gene technology (Österreichische Gentechnikkommission) adopted a set of additional criteria and requirements (Kriterienkatalog) for predictive genetic testing. This Kriterienkatalog is not legally binding but gives guidelines to which relevant institutions and the competent authority should adhere. It is available on the government's home page http://www.gentechnik.gv.at under Rechtliches - Gentechnikbuch.

Belgium

Belgium was one of the first countries in Europe to form a Council for Human Genetics. Since 1973, the "De Hoge Raad voor de Antropogenetica - or "Conseil supérieur de la Génétique humaine" has represented the genetic centers of Belgium in the respective university hospitals. In 1987 the country developed legislation (see below) to restrict genetic counseling and diagnostic testing to these centers. These centers are in general financed by government and are obliged to deliver genetic counseling along with the tests. Genetic services are accessible to everybody who needs them, which means that referral by a physician is not necessary.

Although there exists no formal training program for clinical/medical geneticists in Belgium, a clinical specialization in one of the other medical specialties is strongly advised, together with several years of training in a genetic center, with at least part of the time spent in a molecular and/or cytogenetic laboratory.

- Royal Decree of 14 December 1987 concerning the degree of standards, which have be fulfilled by the centers for human heredity
This decree states that genetic diagnostic testing could only be carried out in the recognized laboratories of the genetic centers. Each recognized genetics center, which performs genetic tests in the accredited laboratory, should in conjunction with the laboratory activities offer clinical diagnostic and genetic counseling services. In addition, each of these centers must provide a detailed activity report on yearly basis for the government. On this condition, the genetic centers receive funding from the government. The 1987 legislation also says that genetic

counseling should be offered on a non-profit, multidisciplinary basis and includes all necessary psychological and moral support to help the individual deal with the information and the implications.

Cyprus

Cyprus has no specific legislation dealing with human genetics yet, and preparatory work in this area is in its early stages. However, Cyprus has subscribed the European Protocol for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine.

Clinical genetic services are provided by public and private centers. Laboratories do not need special accreditation or license to practice in Cyprus and no system for accreditation or licensing has so far been established. Laboratories take part in external quality assessment on an individual basis. There are no formal training programs in genetics by Cypriot academic institutions.

Czech Republic

Czech Republic has no specific legislation dealing with human genetics yet. However, Czech Republic has subscribed the European Protocol for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine.

Clinical genetics has been officially included in the health care system since 1980. There is a strong demand for individual laboratories and departments' accreditation. Systematic postgraduate education in clinical genetics has expended since 1980.

Denmark

In Denmark genetic testing is mainly regulated through the legal framework that applies to the Danish national healthcare system as a whole. Prenatal testing and genetic counselling are conducted in a few selected centres. Cytogenetic testing is performed in laboratories attached to prenatal centres. All investigations are reported to the prenatal cytogenetic central registry. Clinical genetics became a medical specialty in 1997 and genetic counseling is performed by specialists in clinical genetics. DNA testing is performed in clinical genetic and clinical biochemistry departments, mainly in university hospitals. Laboratories do not need special accreditation or license to practice and no system for accreditation or licensing has so far been established. However, laboratories take part in external quality assessment on an individual basis. On the other hand, biobanks of biological materials including genetic material and registries with health information, including genetic information must be registered and approved by the data protection agency. Pharmacogenetic testing in relation to clinical trials of medicines and genetic testing in research projects must be notified to the regional ethical committee for approval prior to initiation of the project. The ethics committee evaluates the information given to the study persons, informed consent, data protection by approval from the data inspection service and information about results to the patients.

In addition, some specific guidelines have been developed, such as the following:

- *Danish Ministry of Health, Guidelines for the Information of Relatives in Hereditary Nonpolyposis Colorectal Cancer (HNPCC testing) (1996)*
- *Danish Council of Ethics, Priority-setting in the Health Service (1997)*
- *Danish Council of Ethics, Report and Recommendations on Presymptomatic Genetic Testing (2000)*
- *Danish HNPCC Registry, Guidelines for Counseling Testing and Follow-Up Programs for NHPPC*
- *Danish Breast Cancer Collaboration Group, Guidelines for Counseling Testing and Follow-Up Programs for BRCA 1 and 2*

In 1992, the Minister of Labour developed a bill banning the use of genetic tests in connection with employment and insurance. The bill (No. L44) denies employers or insurance companies the right to ask for or to use any type

of genetic tests. The bill was further amended by a Law Reform Commission in 1994 and extended to regulate the use of all health information. The bill was endorsed by the Danish Parliament in April 1996.

Estonia

- Act No 1-5/829/1996 on Newborn Screening, Social Ministry, 1996
The organization, performance and availability of newborn screening for phenylketonuria and hypothyreosis are coordinated by this Act.

- Regulation No 33/1997 on Prenatal Diagnostics, Social Ministry, 1997
The performance of prenatal testing, availability and quality control are regulated in this document.

Finland

Genetic testing is carried out in university hospitals and in specialized private laboratories. Although no specific regulations exist on genetic testing, supervision and quality control of both public and private sector laboratories are organized by state authorities. A general quality assessment scheme of genetic testing has so far not been developed. However, a recent Working Party set up by the Ministry of Social Affairs and Health has made recommendations concerning quality assessment, supervision, counseling and use of information in relation to genetic testing. The Ministry will decide on possible legislative measures. There is also a National Advisory Board on Health Care Ethics , since 1998, which can discuss matters in the field of genetic services.

- Act on the Status and Rights of patients, 785/1992
The act regulates i.e. patient's right to be informed about his/her state of health, patient's right to self-determination, drafting and keeping patient documents and confidentiality of information in patient documents. Following the publication of this Act a National Advisory Board on Health Care Ethics (1998) was formed which takes initiatives and releases statements and recommendations on ethical issues in health care.

- Act concerning health care professionals, 559/1994
The aim of the act is to promote the safety of patients and to improve the quality of health care services by ensuring that health care professionals have the necessary training and professional qualifications and by organizing the supervision of health care professionals.

- Gene Technology Act, 377/1995
This act aims to promote the safe use and development of gene technology in an ethically acceptable way, and to prevent and avert any harm to human health. It does, however, not apply to modification of human genetic material by genetic techniques. An Act of this (821/1995) includes the regulations on Advisory Gene Technology Board, which is formed to follow, investigate and give recommendations in the field of biotechnology, including bioethics and genetic testing. An amendment of this Act is in preparation.

- Medical Research Act, 488/2000
This act includes research using human embryos, up to the age of 14 days post conception, by a specific permission from a statutory board. Preimplantation genetic diagnosis is an accepted field of study. An amendment of this act is in preparation, based on the EU Directive of Clinical Drug Trials on Medical Products for Human Use (2001/20/EC).

- Act on the protection of privacy in working life, 477/2001
In section 7 of this act, it states that "the employer has no right to require the employee to take part in genetic testing during recruitment or during the employment relationship, and no right to know whether or not the employee has ever taken part in such testing."

France

- Laws No 94-653 of July 29, 1994 on respect for the human body (http://www.cnrs.fr/SDV/loirespectcorps.html)
This law modifies the Civil Code by introducing notably the notions of the fundamental right to respect for one's body, therapeutic necessity as the only acceptable reason for violating bodily integrity and this only if the individual has consented. Chapter III of the law is devoted to "Genetic characteristics and genetic identification of a person". Article 16-10 states that the genetic study of a person's characteristics may only be undertaken for medical or scientific research purposes. Before such a study is undertaken the person's consent must be secured. Strict penalties are provided if consent has not been obtained (Article 226-25 of the Penal Code) or if the genetic study is carried out for non medical or non scientific purposes (Article 226-26 of the Penal Code). The restriction of genetic testing for medical or scientific purposes has been reaffirmed in the Article L" 145-15 of the new title VI of the Public Health Code (1998).

- National Ethical Consultative Committee for the Life and Health Sciences in France, Genetics and Medicine: From Prediction to Prevention, Paris, 1995 (http://www.ccne-ethique.org/english/avis/)
This report declares the ethical principles that must be respected, with respect to all the activities involved in genetics and medicine. Its recommendations cover the following topics and ethical principles: respect of the autonomy of the subject, respect of medical confidentiality; respect of privacy in computerizing personal data; the use of biological samples; the prohibition of using results of genetic tests for purposes other than medical or scientific; procedures of accreditation of the materials involved in genetic testing; prior evaluation of the impact of the tests; information and formation of all medical personnel in genetics; the need to guarantee correct public information; prohibition of all uses that would contribute to stigmatization or unfair discrimination in the social and economic spheres.

- Decree n. 2000-570 dated June 23, 2000 fixing the conditions of prescription and implementation of genetic characteristics and genetic identification investigations of a person for medical reasons and modifying the Public Health Code
This decree delineates 5 conditions for prescribing and implementing genetic testing for medical purposes: 1) Condition of prescription; 2) Condition of approval from appropriate authorities both for clinicians and laboratories; 3) Conditions of reporting results; 4) Conditions of medical record protection; and 5) Approval from the National Consultative Commission created for this purpose.

Art. R. 1131-1 states the regulatory difference between 'diagnostic tests' in symptomatic individuals and 'predictive tests' in asymptomatic individuals.

Physicians responsible for this genetic analysis must be qualified in medical biology or biology-pharmacology. Exceptionally, a senior scientist (non-MD) may be responsible for these genetic analyses only if he/she has experience on cytogenetics or molecular biology. A consultative Commission must be asked to rule on the necessity of such procedures and on their implementation.

-National Consultative Ethics Committee, No. 70, Consent for the benefit of another person, 2001 (http://www.ccne-ethique.fr/english/start.htm)
In this opinion, the National Consultative Ethics Committee opposes the legal and the ethical considerations on this topic. It considers that consent in favour of, or for the benefit of a third party, leads to several principles, possibly conflicting, being considered: the autonomy of the index person, benevolence in favour of a third party, and solidarity. In the last analysis, the committe consider that educating society to a better understanding of the meaning of solidarity, is a means of respecting individuals by calling on their sense of responsibility, and informing them on the purpose and altruism of a decision. To consent in the interest of another person is to be both separate and responsible.

- Law no 2002-303 of March 4, 2002 relating to the rights of the patients and the quality of the health care system (http://www.assembleenat.fr/dossiers/droits_des_malades.asp)
The goals of this act is :
- To develop the medical democracy (first title) by recognizing rights for any person in its relationships with the health care system, by granting rights to the users and by associating them to the operation of the health care system, and by allowing the development of policies of health at the national and regional levels;

- To improve quality of the health care system (title II) by developing competences of the professionals, the continuous medical training and an global prevention policy;
- To allow the repair of the medical risks (title III) by improving the insurance access, by defining the principles of the medical responsibility and by creating procedures for amicable agreement and for the compensation of the medical accident victims.
- Art. L. 1141-1 states that insurers cannot take in account constitutional genetic testing for their offer (life or disabilities insurances) even if the results of such a test are disclosed by the insurance-seeker

- *National Consultative Ethics Committee, No. 76, Regarding the obligation to disclose genetic information of concern to the family in the event of medical necessity (2003-04-24), 2003 (http://www.ccne-ethique.fr/english/start.htm)*
This document discusses that the most effective way to do this is by "protecting the family whilst strictly preserving personal privacy, [and] to implement adequate procedures within the bounds of strict observance of medical confidentiality." It considers this as a moral duty, and that it should not be a legal one.

- *National Consultative Ethics Committee, No. 79 Transposition in French law of the European directive relating to clinical trials of drugs : a new ethical framework for human research, (2003-09-18), 2003(http://www.ccne-ethique.fr/english/start.htm)*

Germany

As regards the application of genetic testing, professional organizations and vocational associations have issued a large number of comments and guidelines (see below). These comments and guidelines are based on the principles of counseling and education, autonomy and confidentiality. Strictly speaking, they do not have a legally binding character, but are only recommendations to their members. However, there could be legal implications should medical treatment with adverse consequences be due to a violation of professional guidelines.

- *The German Bundestag, Chancen und Risken der Gentechnologie Enquete-Commission, 1987*
Prenatal diagnosis and newborn screening programs were accepted. The report contained detailed recommendations on the consent and counseling requirements, which must be fulfilled before any genetic test can be carried out. In most instances the report did not recommend that legislation be enacted but rather that these matters be supervised by authoritative professional bodies.

- *The German Society of Human Genetics, Statement on postnatal predictive genetic testing, 1991 (http://gfhev.de/kommission/index.html)*
Predictive genetic testing must take, among other things, the following into consideration: 1) “Comprehensive information must be offered to all concerned persons, and counseling about alternative options must be guaranteed”. (…) 3) “Explanation and counseling about available tests must be non directive. 4) Predictive genetic diagnosis may be performed only for persons of legal age. Exceptions are for disorders for which preventive or therapeutic measures could be initiated in childhood”. (…) 6) “Predictive genetic diagnosis must not become a routine investigation. When developing guidelines, the expectations of the affected should be extensively considered as was done internationally. (…) Since manifold problems are foreseeable, predictive genetic diagnosis should be introduced only within the framework of a scientifically accompanying pilot project. Due to their limited personnel and equipment and in spite of professional competence, human genetics institutes and genetic counseling facilities presently are able in only a limited way to guarantee that predictive genetic diagnosis is carried out within the required framework. However, attempts should be made to establish this type of diagnosis including the required counseling, at qualified non profit institutions”.

- *The German Society of Human Genetics, Statement on carrier screening, 1991 (http://gfhev.de/kommission/index.html)*

- The German Society of Human Genetics, Curriculum for non-MD human geneticists, 1993, 1994 (http://gfhev.de/kommission/index.html)

- The Board of Medical Genetics, Patient information, Informed consent for genetic counseling, 1994

- The Board of Medical Genetics, Statement and Recommendation on confidentiality, 1995

- The German Society of Human Genetics, Statement on genetic diagnosis in childhood and adolescence, 1995 (http://gfhev.de/kommission/index.html)

"Genetic diagnosis in children and adolescents is indicated if it is necessary for the differential diagnosis of manifest symptoms or for establishing the etiology of a disease. A predictive genetic diagnosis is indicated during childhood if the onset of a disorder can be regularly expected at this age and if medical measures can be taken to prevent the disease or its complications or to treat the disease. (…) However, deferring a predictive genetic diagnostic test should not prevent discussing the disease in question with the child in a manner appropriate to his/her age, including how it is inherited and the possibility of its being diagnosed. (…) An investigation for the sole purpose of determining the carrier status for a recessive inherited illness or a balanced familial chromosomal translocation should not be carried out since the results would only be significant for future reproductive decisions of the child him/herself. Therefore the examination should be deferred until the child can understand all the associated facts and psychosocial implications and asks for the test him/herself."

- The German Society of Human Genetics, Position Paper, 1996 (http://gfhev.de/kommission/index.html)

This paper defines standards for the application of genetic tests to nearly all fields of practical genetics. Concerning access and use of genetic services, "all population groups should have similar access to genetic information, counseling, and diagnostic services. Information should be generally available, appropriate, and qualified, and counseling and examination capacities must be adequate. Because of the impact of genetic diagnoses, utilization of genetic counseling and diagnosis should occur on a voluntary basis only. (…) Thus, everyone has the right not to know about his or her own genetic make-up. Likewise, no one should be prevented from using genetic counseling and diagnostic services. Individuals who utilize certain genetic examinations, but also persons who refuse to utilize them are in danger of being stigmatized or discriminated against. Such tendencies of public opinion must be counteracted by increased efforts to inform and educate the public. (…) At this time, the only known exception to the principle that the utilization of diagnostic genetic tests be voluntary is the routine examination of newborns for genetically determined disorders that are amenable to early treatment or prevention."

- The Board of Medical Genetics, The German Society of Human Genetics, Declaration, Curriculum on Education in ethical and psychological dimensions of genetic counseling, 1996

- The Board of Medical Genetics, Guidelines on genetic counseling, 1996

- The Board of Medical Genetics, Guidelines on tumor cytogenetic testing, 1996

- The Board of Medical Genetics, Guidelines on molecular genetic testing, 1996

- The Board of Medical Genetics, Guidelines on cytogenetic testing, 1997

- The German Medical Association, Guidelines on predictive genetic testing for tumor disposition, 1998

-Voluntary formal commitment of member companies of the German Insurance Association, 2003 (Gesamtverband der Deutschen Versicherungswirtschaft e. V. - GDV) (http://www.gdv.de/english/index.html)

In discussions with the German government, they have developed a self commitment (Code of practice) for predictive genetic testing. Both German life insurers and private health insurers commit themselves not to order

any predictive genetic testing, nor to take predictive genetic testing into consideration for risk assessment, except for high sum insured.

- *The German Medical Association, Guidelines on predictive genetic testing, 2003, (http://www.bundesaerztekammer.de/30/Richtlinien/Richtidx/Praediktiv/PraedDiagnostik.pdf)*
The main points of the guidelines are: predictive genetic testing must be "embedded" in genetic counseling, predictive genetic testing is a medical act, and predictive testing requires fully informed subjects.

-*Federal government bill regulating genetic testing, Genetestgesetz, in preparation*
This bill indicates that a genetic test is a medical act.

Greece

Although the first law on the regulation of the practice of medical genetics was passed by the Greek parliament in 1980, it was never implemented. A special advisory committee was formed in the Central Health Council of the Ministry of Health and its proposals for the development of genetics centers and the specialty of genetics are being studied by the Ministry in order to be incorporated in a forthcoming Health Bill. However to date Medical Genetics is not recognized as a specialty in Greece.

Medical genetics has entered the university curriculum as an integral part of medical and nursing studies, through the establishment of a department of genetics in the medical school and the teaching of the medical genetics and genetic counseling at the undergraduate, graduate and post-graduate level in both medical and nursing faculties respectively.

With respect to higher education, although there is a Medical Genetics department in the Medical School of Athens University, the subject of medical genetics is not currently taught as a core subject in undergraduate medical studies. Also, clinical genetics is taught as an elective in the Medical School of Athens University, and not as part of the core curriculum. However, some aspects of molecular genetics are covered by the biology core of undergraduate studies in all medical schools. The same applies in the Nursing School of Athens University in which there is also a postgraduate course for genetic counseling.

With respect to genetic services, a few public and private laboratories have joined the European Molecular Genetics Quality Network, and one private cytogenetics laboratory has joined a quality control scheme abroad. At present, genetic counseling is performed at certain university and public genetic units by clinical geneticists or privately, mostly for specifically referred cases.

The proposal to the Ministry of Health is for the development of genetic units in all university and district hospitals according to the Council of Europe guidelines.

Hungary

There are no approved guidelines for genetic testing in Hungary. Professionals in university or municipal hospitals are delivering services according to practice based on medical literature, nation-wide and international experience in genetic counseling and discussions at scientific meetings. Medical genetic services and genetic research are regulated by some relevant paragraphs of the law on health (No. CLIV, 1997), and by the departmental order of the Ministry of Health on biomedical research. In 1999, an Ad Hoc Committee was named by the Ministry of Health to develop guidelines for genetic screening and testing in Hungary. This resulted in a background document called, "On the protection of human genetic data, regulation of genetic tests and screening, genetic research, and biobanking" which was released for public discussion on February 10, 2004. According to the schedule of the Ministry of Health, the material will be introduced to the Parliament for ratification in May, 2004.

No agency has jurisdiction over clearing diagnostic services for marketing. However, there is occasional collaboration between service delivery units and industry which supplies kits for which licensing has been obtained.

-*Hungarian Parliament, Oviedo's Convention on Human Rights and Biomedicine, 2002 (No. VI. of 2002)*

Iceland

Iceland has no law that specifically deals with human genetics.

- *Act n. 97/1990 on a Healthcare Services, Ministry of Health, 1990 (http://brunnur.stjr.is/interpro/htr/htr.nsf)*
The health sector is regulated according to this Health Service Act by which all inhabitants have right of access to the best possible health service at any given time for the protection of their mental, social and physical health.

- *Act n. 74/1997 on the Rights of Patients, Ministry of Health, 1997 (http://brunnur.stjr.is/interpro/htr/htr.nsf)*
This Act includes fundamental rights of patients including rules on consent, confidentiality and handling of information in clinical records.

- *Act n. 139/1998 on a Health Sector Database, Ministry of Health, 1998 (http://brunnur.stjr.is/interpro/htr/htr.nsf)*
This Act is in compliance with the Act on the Rights of Patients. By reference to article 29 in the Act on the Rights of Patients, the Minister of Health and Social Security has issued a regulation on scientific research in the health sector (Reg. No 552/1999).

The Act on a Health Sector Database makes it legal for a private company to construct an electronic database of non-personally identifiable health data with the aim of increasing knowledge in order to improve health and health services. The Act makes it possible to combine and analyze health data with genetic and genealogical data.

Ireland

Ireland has no law specifically dealing with human genetics and Ireland has not signed the 1997 Oviedo Bioethics Convention. Clinical Genetics is a specialty recognized by the Irish Medical Council, and clinical practice is subject to General Medical Council guidelines. A Department of Health committee is currently considering guidelines for assisted reproductive practice, including preimplantation genetic diagnosis.

Ireland has been involved with the UK (Clinical Molecular Genetics Society) and the Netherlands in developing laboratory guidelines for molecular genetic testing for specific diseases. These guidelines have been adopted by the European Molecular Genetics Quality Network (EMQN) (http://www.emqn.org).

Italy

- *The Italian Committee on Bioethics, The human Genome Project, 18 March, 1994*

- *National Council of the Federation of the Colleges of Physicians and Dentists, the new Italian code of medical ethics, 1995*
In this code, article 42 address interventions on genome and conceptuses.

- *National Guidelines for Genetic Testing, Linee guida per test genetici, 1998*
In 1998, National Guidelines for Genetic Testing were prepared by a Task Force appointed by the National Committee for Biosecurity and Biotechnologies, coordinated by the National Health Institute. The general objectives are: 1) ensuring the safety and effectiveness of both existing and newly introduced genetic tests; 2) defining the criteria for quality assurance of laboratories performing genetic tests; 3) ensuring both adequate

counseling and the free decision of individuals and families; this will include a particular attention to problems concerning ethics and privacy. Some topics deserving a specific concern have been identified, namely: genetic testing for prenatal diagnosis, genetic testing for susceptibility to cancer and genetic testing for rare diseases. There is no law for preimplantation genetic diagnosis.

- Cytogenetic and Molecular Testing in Italy, ISTISAN Reports no.20, 1998

- The Italian Committee on Bioethics, Orientamenti bioetici per i test genetici, 19 November 1999 (http://www.palazzochigi.it/bioetica/orientamenti%20biomedici.htm)

Lithuania

- Act No 136/1991, Ministry of Health
In 1991 a University Hospital Human Genetics Center (Vilnius) was created. The activities of the Center focus on the prevention of inherited diseases, including genetic counseling, neonatal screening for PKU and for congenital hypothyroidism, registration of congenital anomalies and prenatal diagnosis as well as education in human and clinical genetics for medical students. Residentship in clinical genetics was introduced in 1992. The Center takes part in external quality assessment of newborn screening for PKU and congenital hypothyroidism since 1996, Huntington disease since 1998, and Duchenne muscula dystrophy and cystic fibrosis since 2000.

- Act No 199/1991, Ministry of Health
Clinical genetics became a medical specialty and genetic counseling is performed by specialists in clinical genetics (MD).

- Act No 706/1997, Ministry of Health
This Act regulates national standards for genetic counseling and professional responsibilities of clinical geneticists.

- Act No 354/2000, Ministry of Health
The main activities of the Vilnius University Hospital Human Genetics Center are being performed according to the program "The structure, defects, and protection of gene pool of the Lithuanian population".

- Act No VIII-1679/2000, Lithuanian Parliament
This law on Bioethics regulates genetic testing. Genetic testing can only be carried out for medical or scientific purposes and only after written consent has been obtained from the individual.

Norway

- Act Relating to the Application of Biotechnology in Medicine, Law n. 56 of 5 August 1994 (http://www.helsetilsynet.no/htil/avd2/bio_act.htm)
This Act gives a frame of general guidelines for assisted reproductive technology applications, research on embryos, preimplantation diagnosis, prenatal diagnosis, genetic testing after birth and gene therapy. This Act also specifies obligations about authorization of institutions applying medical biotechnology and the duty for such institutions to report regularly on their activities to the Ministry of Health and Social Affairs.

Genetic testing for diagnostic purposes is permitted without restrictions, but the law requires that comprehensive genetic counseling be given before, during and after genetic tests performed on healthy persons for presymptomatic, predictive or carrier purposes. Presymptomatic, predictive and carrier testing is limited to individuals above the age of 16 years. When the information refers to a diagnostic test, genetic results may be communicated, without restrictions, between medical institutions authorized to apply medical biotechnology. However, the exchange of genetic information about presymptomatic, predictive or carrier tests is restricted. The Act states that it is prohibited to ask whether a presymptomatic, predictive or carrier test has been performed.

Portugal

The Ratification of the "Convention for the Protection of Human Rights and Dignity of the Human Being and the additional protocol on the prohibition of reproductive cloning" was published in January 2001. Guidelines prepared by a task force were also published in 1997 by the Ministry of Health. These guidelines are concerned with the ethical and professional rules on prenatal diagnosis and genetic testing, namely confidentiality, genetic counseling and genetic testing of children. Genetic counseling before testing late onset diseases (Machado - Joseph and Familial Amiloid Polineuropathy) is usually offered but not always on recessive carriers familial testing and oncologic diseases. The specialty of medical genetics has been formally recognized in April of 1998. The five years training for medical geneticists began in 2001.

Quality assessment schemes for laboratory genetic services are not obligatory. Since 1994, Portuguese laboratories have participated in the European EQA of the European Molecular Genetics Quality Network for cystic fibrosis, Friedensreich´s ataxia, Huntington disease and Duchenne muscular dystrophy.

- *Despacho Ministerial No 9108/97, Guidelines for Molecular Genetic Diagnosis*

Russia

- *Ministry of Health, On Further Development of Medical Genetic Services in the Russian Federation, Circular n. 316, December 12, 1993.*

All medical genetic services in Russia are mandated by the principal circular n. 316 issued by the ministry of Health on December 12, 1993 - "On Further Development of Medical Genetic Services in the Russian Federation". Revised and updated version of this circular has been prepared. Regulations govern diagnosis at each medical genetic level, the interrelationships between different levels, and the type of diagnostic procedures and basic equipment. Genetic counseling and prenatal diagnostics services are basic subjects of these circulars. There are no officially approved guidelines for predictive genetic testing.

Genetics is recognized as a medical specialty. Basic education in medical genetics is provided in all medical schools and also in medical faculties of many universities.

Spain

There are no approved guidelines for genetic testing in Spain. Consent to undergo any medical tests is granted through General Health Law of 25 April 1986. The Organic Law regulating the automated processing and protection of personal data of 13 December 1999 provides special measures of protection for personal health data.

Quality assessment schemes for genetic services have been addressed in specific areas. In 1996 standard criteria for quality control of cytogenetic and prenatal diagnosis laboratories were issued and currently there are plans to develop quality standards for clinical and molecular genetic services.

In 1999, Spain subscribed and joined the European Agreement for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine.

- *General Health Law of 25 April 1986*

- *The Organic Law regulating the automated processing of personal data of 29 October 1992*

  The Organic Law regulating the automated processing of personal data of 29 October 1992 provides special measures of protection for personal health data (articles 7.3 and 8).

- *The Organic Law regulating the automated processing and protection of personal data of 13 December 1999*

This law includes automated data and any type of personal data.

Sweden

- Law 114 of March 1991 on the Use of Certain Gene Technologies within the Context of General Medical Examinations (1993)
This law examines the use of certain genetic technology in medical examinations. There must be permission from the National Board of Health and Welfare. Authorization from this body is required before DNA testing can be carried out. This requirement extends to the use of genetic techniques for diagnostic purposes.

- Swedish Society for Medical Genetics, 1994
The Swedish Society for Medical Genetics has brought forward a quality assessment document for clinical genetic units including guidelines for cytogenetic and molecular routines as well as for genetic counseling. This document has been adopted by all the university clinical genetic departments as a minimum standard for quality.

- National Board of Health and Social Welfare, Genetics and Genetechnology in Health Care. State-of-the-Art and Guidelines for Ethical Considerations, 1999

-Parlimentary committee on genetic integrity, final report: Statens Offentliga Utredningar, SOU 2004:20. Genetik, Integritet, och etik, 2004.
(http://social.regeringen.se/propositionermm/sou/pdf/sou2004/sou2004_20a.pdf)
This committee was mandated to review issues relating to genetic diagnosis, gene therapy and cloning. This document also touches on the fundamental issues regarding genetic information, and why it has a status separate from other information. They believe it should be forbidden for employers to request genetic information, and also for insurance companies, except for "risky personal insurance policies involving very large sums of money." The committee proposes a new law on genetic integrity. When discussing who should be allowed to carry out genetic tests, they discuss that it is probably not feasible to place supervision of labs under a Swedish public body, and propose that 'self-test' kits should be regulated by the medical devices act. This document also discusses genetic tests and information in regards to health service and medical care, and the areas where more genetic education is needed of health care professionals and the general public. The committee also ratifies the Council of Europe's Convention on Human Rights and Biomedicine (except it has reservations with article 18.2 regarding the prohibition of the creation of human embryos for research). They state that their proposed statutes should come into force on 1 July 2005.

Switzerland

- The Swiss Federal Constitution, 1992
The Constitution provides rulings on human genetic practice and medical-assisted procreation. Article 119 (introduced in 1992 as article 24novies, old numbering) paragraph 2 states that the genetic make-up of an individual may be investigated, registered or divulged only with his/her consent or on the basis of a legal prescription.

- The Swiss Academy of Medical Sciences, Medical-ethical Guidelines for Genetic Investigations in Humans, Approved by the Senate of the Swiss Academy of Medical Sciences on 3rd June 1993 (http://www.samw.ch/e/richtlinien/richtlinien_fs.html)
The Swiss Academy of Medical Sciences guidelines are not legally binding, unless cantonal legislation gives them binding force. According to the guidelines, genetic investigations are ethically justified if they serve the following purposes: determination of a predisposition for a hereditary disease or handicap, with a view to appropriate planning for the life of the individual, and family planning; or detection of a predisposition for a particular disease when symptoms have not yet appeared, if effective measures can be taken to alleviate and prevent severe effects of the disease or if the result of the investigation is of immediate relevance for planning for the life of the individual or for family planning. Genetic investigations must be accompanied by appropriate, non-directive counseling before, during and after the investigation. The decision to carry out, continue or stop the investigation rests exclusively with the patient, who will also decide whether and to what extent he wishes to

be informed of, and to draw conclusions from, the result of the investigation. The voluntary nature of participation in the investigation and the right not to be informed of the result must also be guaranteed.

-*Swiss Parliment, Loi fédérale sur l'analyse génétique humaine, 2003*
This law on genetic testing is currently (as of February 2004) being discussed in parliment. It is a penal law regulating and containing the following paragraphs:
(1.) Scope of the law, purposes and concepts (2.) Basic issues of genetic testing: prohibition of discrimination, informed choice, the right 'not to know,' protection of genetic data, registration for laboratories providing genetic testing by the Swiss Federal Office of Public Health (SFOPH), in-vitro diagnostic kits for genetic testing (3.) Genetic testing in medicine: on persons in general, prenatal diagnosis (including all other methods on prenatal testing as well), population screening, requirements to meet previous to genetic testing, genetic counselling, counselling previous to prenatal testing, information to be given concerning embryonal/fetal risk-testing in pregnancy, introduction of counselling services/availability of counselling services, right of autonomy of decision making, disclosure (4.) Genetic testing and employment (5.) Genetic testing and insurances (6.) Genetic testing for liability (7.) DNA - profiling for investigations of descent (8.) Introduction / appointment of a committee of experts concerning issues of genetic testing (9.) Penalties (10.) Concluding regulations

-*Federal Office of Health, Loi fédérale sur la recherche de l'être humaine -in discussion, 2004*
This project of a law will contain various issues on research in humans that have not been regulated up to now elsewhere in an existing law. There is a taskforce that is currently working at a proposition of such a law and at the present time it is still confidential. However, the following are some issues that were discussed in a public forum regarding this project, in early 2004:

Protection of probands in research projects in general, in minors and dependent persons, data protection, promotion of research and approval of projects, how to promote research in specific groups of interest e.g. rare diseases, children, pregnant women, financing of research projects, availability of research results, promotion of research concerning ethical, psychological, socio-cultural and legal issues of research projects (ELSI research)

The Netherlands

In the Netherlands, genetic services are incorporated in the health care and funded in such a way that equal access is guaranteed. The quality of the genetic services is ensured by legislation requiring a license from the government (only 8 centers are licensed and funded by the health insurers). Also the close organizational contact of clinical genetics with research groups of human genetics in medical faculty enable a timely update / introduction of new diagnostic technologies.

As far as legislation is concerned there are regulatory frameworks for the licensing of clinical genetics centers as well as the limitation of unlimited growth of activities and commercial testing. As of recently, there is a law protecting individuals against the request of genetic testing (or information) by third parties. Also, a document on the application of genetics in health care has been published by the Dutch Ministry of Health. This document comments on future organization of genetic services and predictive DNA testing and on various psychosocial and ethical issues related to screening, family counseling and presymptomatic DNA testing. Most of the government's views are in accordance with recommendations by the Dutch Health Council in its advice "DNA diagnostics in health care" (May 1998).

- *The Health Council of the Netherlands, Report: Heredity, Science and Society: On the possibility and Limits of Genetic Testing and Gene Therapy, The Hague, 1989*
The Council takes a strong position on autonomy, suggesting that every individual owns his or her genetic material and therefore informed consent is necessary for any use of it. However, the physician-patient relationship is regarded as one in which the physician's role cannot be specified entirely in terms of satisfying the interests of the patient. The physician has his or her own responsibilities (e.g., to other parties), which lead to a potential conflict between beneficence and autonomy. The council is of the view that unauthorized disclosure

may be permissible under limited circumstances when serious harm can be avoided and has noted that relatives' right to privacy should be a consideration when deciding whether or not a disclosure should be made.

- *The Health Council of the Netherlands: Committee Genetic Screening, Genetic Screening, The Hague, 1994*
This committee has listed criteria which must be met by genetic screening programs prior their implementation. The Dutch Health Council defines genetic screening as "any kind of test performed for the systematic early detection or exclusion of a hereditary disease, the predisposition to such a disease or to determine whether a person carries a predisposition which may produce a hereditary disease in offspring". The Council states that "the program for the early detection and treatment of diseases should involve an important health problem". However, according to the Council, "it is up to the individual and parents to determine whether a condition is serious enough to enter a screening program"; genetic screening aims "to enable people to achieve greater autonomy and to decide upon a course of action that is acceptable to them. Voluntary participation based on well-understood information is an absolute requirement and there must be safeguards for free individuals choice during the whole screening process". Counseling is also considered important.

- *The Population Screening Act, 1992 (1996)*
This act states that screening by means of ionizing radiation, screening for cancer and screening for serious disorders for which there is no treatment are not allowed without ministerial approval, based on the advice and assessment of the Health Council. A license may be refused if the screening program is scientifically unsound, if it conflicts with statutory regulations or if the risks are found to outweigh any benefits.

- *The Health Council of the Netherlands, Advisory Report on DNA Diagnostics in Health Care, Publication N. 1998/11 1998*
Genetic research provides new opportunities for predicting the occurrence of disease, which were discussed in this report.

- *The Health Council of the Netherlands, Advisory Report on Clinical Genetic Testing and Counseling, Publication N. 1999/07, 1999*
According to this report, regulations on clinical genetic testing and counseling in the Netherlands apply to "postnatal and prenatal chromosome, biochemical and DNA testing, the clinical removal of fetal material, advanced ultrasound scanning for fetal abnormalities and complex genetic counseling". The regulations are designed to assure the quality and continuity of the procedures in question, which are regarded as a form of medical care.

The report makes the following recommendations: 1) Genetic counseling and the associated test activities should continue to be concentrated in the nominated centers. 2) The professional groups involved in clinical genetics should have responsibility for drafting and updating quality requirements; in this context, the government's role should be supervisory. 3) Forecasts of the level of provision required in this field should take account of the rapid increase in demand for counseling for hereditary forms of cancer. 4) In addition to the Standing Committee on Genetics, several professional organizations are involved in developing best practice guidelines, including the clinical genetics centers. The centers' activities are regulated by a single package of legislation (Section 2 of the Special Medical Treatments Act).

-*Ministry of Health, Regulation on clinical genetic testing and counseling, 2003*
The regulation confirms that clinical genetic testing and counseling requires a license from the ministry, and expands this stipulation to pre-implantation genetic diagnosis. Only 8 clinical genetic centers in the country are licenced to perform clinical genetic testing and counseling, and only one center is licenced for pre-implantation genetic diagnosis. The clinical genetic centers are summoned to take initiatives to become regional centers of expertise in order to develop a network which has, as its most important function, the task to stimulate and monitor the quality of care outside the centers.

Turkey

Genetic testing is undertaken by molecular genetic units mostly in university hospitals and recently in a limited number of private laboratories. The formulation of the genetic screening programs by the Ministry of Health and Social Affairs is very new and therefore the regulations for each screening program is going to be performed day by day. However, some of the genetic screening programs are being performed individually by the genetic diagnosis centers.

- *The Regulation of the Genetic Diagnosis Centers (1998, No: 23368) (Genetik Tani Merkezleri Yönetmeligi)*
This regulation is about the best practice standards of the centers of both the public sector and the private laboratories. The quality control and standardization of analysis are not included in this regulation. These are controlled by the Turkish Association of Medical Genetics Committee.

United Kingdom

An Advisory Committee on Genetic Testing (ACGT) was established in 1996. Its role was to advise UK Health Ministers on developments in genetic testing, on the ethical, social and scientific aspects of testing, and on the requirements to be met by suppliers of genetic testing services. It also considered the use, or potential use, of tests both for clinical practice and for those supplied directly to the public. ACGT has published two reports which are relevant to the provision of genetic services: 1) a code of practice and guidance on genetic testing services supplied direct to the public (1997), and 2) a report on genetic testing for late-onset disorders (1998) (see below). The work of the ACGT has now been transferred to the Human Genetics Commission (which was established in 1999).

*-Department of Health White Paper, Our inheritance, our future – realizing the potential of genetics in the NHS, 2003 (*http://www.doh.gov.uk/genetics/whitepaper.htm)
'Its aim is to set out a vision of how patients could benefit in future from advances in genetics, and raise awareness of the potential of genetics in healthcare. It sets out a comprehensive plan for preparing the NHS, including the investment of £50 million of new money over the next three years to help realise the benefits of genetics in healthcare (...) This plan will be reviewed in 3 years' time. (...) New initiatives include: (1) a substantial investment in upgrading genetics laboratories, and a boost to the genetics workforce: more genetics counsellors, consultants and laboratory scientists (2) More than £7 million on new initiatives to introduce genetics-based healthcare into mainstream NHS services (3) A new Genetics Education and Development Centre to spearhead education and training in genetics for all healthcare staff (4) New research programmes in pharmacogenetics, gene therapy and health services research to help turn the science into real patient benefit. (...) The White Paper also sets out the safeguards and controls against inappropriate or unsafe use of developments in genetics. In addition to existing controls on gene therapy and use of genetic test results by insurance companies, the government will introduce new legislation to ban DNA theft: it will become an offence to test someone's DNA without their consent except for medical or police purposes. Government also recognises the importance of openness and public debate, and will continue to be responsive to new developments and shifts in public attitudes.'

Other government and non-government advisory groups have also discussed the current organization and commissioning of genetic services, and options for the future. They are presented below.

- *House of Commons Select Committee on Science and Technology, human Genetics: the Science and Its Consequences, Third Report, HMSO, 1995 (http://www.parliament.the-stationery-office.co.uk/pa/cm199899/cmselect/cmsctech/489/48902.htm)*
This report examines the ethical issues arising from genetic technology and recommends the setting up of a Human Genetics Commission to regulate the advance of genetic technology.

- The Genetics Research Advisory Group, A first report to the NHS Central Research and Development Group on the new genetics, Department of Health, 1995
Service implications are discussed in the areas of: 1) The role of the regional genetics services (a role in training and education is stressed); 2) Maintenance of genetic registers; 3) The role of general practice in genetic services; 4) The appropriate organizational structure for a future era involving large-scale genetic testing and screening; and 5) Funding and patents.

- The Genetics Research Advisory Group, The Genetics of Common Diseases. A second report to the NHS Central Research and Development Group on the new genetics, Department of Health, 1995
The report summarizes the current situation of clinical genetics services, discusses the financial implications of new genetics advances, and makes recommendations including: encouraging and coordinating research partnerships to carry out further research in genetic epidemiology, mutation detection techniques, full evaluation of genetic screening and its outcomes, and models of service organization; a systematic approach to the adoption of approved genetic screening schemes; the development of the role of primary care in genetic screening and counseling; education and training programs for professionals and the public; and a survey of existing genetic registers and their functions and effectiveness.

- The Royal College of Physicians of London, Clinical Genetic services into the 21st century, Report of the Committee on Clinical Genetics, London, 1996 (www.rcplondon.ac.uk/pubs/index.html)
This report reviews the current situation and trends in: the nature of clinical genetic services; manpower in clinical genetics; the aims of medical genetics and the role of the clinical geneticist; the relationship between clinical genetics and other medical specialties. This report makes predictions and recommendations for the role of the clinical geneticist in the 21st century, the number of clinical geneticist and related posts that will be needed, the associated training requirements, and the organizational basis for clinical genetic services.

- The Advisory Committee of Genetic Testing, Code of Practice and Guidance on Human Genetic Testing Services Supplied Direct to the Public, 1997 (http://www.open.gov.uk/doh/genetics.htm)
The Committee recognizes that medical practitioners in the National Health Service and private practice, and the commercial sector have roles to play in the provision of genetic testing services. The committee wishes to ensure that such services are delivered with the best interests of those tested in mind and that appropriate information and genetic consultation are available. Therefore, the Committee wishes to ensure that before introduction of services direct to the public, suppliers present their proposal to the Advisory Committee of Genetic Testing. The Committee will consider and monitor testing services in the light of the Code of Practice and Guidance.

- The Advisory Committee on Genetic Testing, A report on Genetic Testing for Late Onset Disorders, 1998 (http://www.open.gov.uk/doh/genetics.htm)
The Committee sets out the issues to be considered before genetic testing for late onset disorders is offered and during the provision of such tests. Before any genetic test is used in clinical practice the scientific and clinical validity should be established. All laboratories providing genetic testing services should be closely linked with other genetic services, and be appropriately accredited for this.

Information on the disorder being tested for should be full, accurate and appropriately presented, in a clear and simple manner that is readily understandable. Appropriate support in preparation for and subsequent to genetic testing should be considered as part of the genetic testing process. In the case of presymptomatic genetic testing of healthy individuals, written consent should always be obtained. Tests for late onset disorders should not be supplied direct to the public.

- The NHS, Commissioning in the new NHS commissioning services 1999-2000, London, 1998 (http://tap.ccta.gov.uk/doh/coin4.nsf/)
This document, issued by the NHS Executive, sets out the new arrangements for commissioning through Long Term Service Agreements. It includes arrangements for commissioning specialist services, which include clinical and laboratory genetic services.

- *The Royal College of Physicians, Commissioning clinical genetic services, Report from the Clinical Genetics Committee, London, 1998 (www.rcplondon.ac.uk/pubs/index.html)*
This report sets out the requirements of a good clinical genetics service, and makes recommendations about how these requirements can best be met by commissioning bodies. It considers: the activities of clinical genetic services, the facilities required, the organization of services, commissioning mechanisms, management arrangements, costing, quality and performance indicators, and genetic services for common disorders.

- *The Royal College of Physicians, Clinical genetic Services. Outcome, effectiveness, quality, Report from the Clinical Genetics Committee, London, 1998 (www.rcplondon.ac.uk/pubs/index.html)*
This report makes recommendations on the collection, storage, and retrieval of genetic data, the use of the outlined quality criteria in assessing effectiveness, and as the basis of service specifications, the need for multidisciplinary research to develop criteria for assessing the intangible outcomes and effectiveness of genetic counseling.

- *The Royal College of Physicians, Retention of Medical Records with Particular Reference to Medical Genetics, London, 1998*

- *Genetic Interest Group, Confidentiality Guidelines, London, G.I.G., 1998 (http://www.gig.org.uk/docs/gig_confidentiality.pdf)*
The purpose of these guidelines is to current practice in medical genetics in the UK with reference to individual confidentiality ; to discuss ethical issues relating to the shared use of individual genetic information within families ; to propose a framework to guide professionnals which formalises existing practice and to suggests a mechanism for resolving "difficult" situations.

- *Genetic Interest Group, Guidelines for Genetic Services, London, G.I.G., 1998 (http://www.gig.org.uk)*
The purpose of these guidelines is to help genetic and other service providers and commissioners, in partnership with service users, set and monitor standards, identify areas for improvement, devise strategies to develop and improve the services, and plan for the future. They cover: availability (service organization, staffing levels, funding), access and equity (referral arrangements, professional and public awareness, access for young people, people with disabilities, ethic minorities), partnerships with user and support groups and with other health professionals and services, good practice in providing information on genetic tests and diagnosis, good practice in genetic counseling (aims, content and scope, procedures, follow-up, confidentiality), long-term follow-up in families, standards for clinical and laboratory services monitoring and evaluation planning for the future.

- *Department of Health, Genetics and Insurance Committee, GAIC, began 1999 (http://www.doh.gov.uk/genetics/gaic/index.htm)*
'GAIC is a non-statutory advisory non-departmental public body and has a UK-wide remit, with terms of reference: (1) to develop and publish criteria for the evaluation of specific genetic tests, their application to particular conditions and their reliability and relevance to particular types of insurance; (2) to evaluate particular tests against those criteria and to bring to public knowledge its findings; (3) to report to Health, Treasury, and Department of Trade and Industry Ministers on proposals received by GAIC from insurance providers and the subsequent level of compliance by the industry with the recommendations of GAIC; (4) to provide independent wide ranging oversight of how insurers are using genetic tests (...) [The latter point] specifically: (a) to provide independent scrutiny of compliance with the ABI Code of Practice and the terms of the 5-year moratorium agreed in 2001 on the use of genetic test results by insurance companies; (b) to consider complaints from insurance applicants about the way an insurance company has dealt with their application under the moratorium, where such complaints have not been resolved to the satisfaction of the applicant by either their insurance company in the first instance or by the ABI; and (c) to report annually to Health, Treasury, and Department of Trade and Industry Ministers on compliance by insurers with the ABI Code of Practice and the moratorium. '

- *The Clinical Genetics Society, The role of the clinical geneticist, 2000*

This discussion paper produced by the Clinical Genetics Society documents the responsibilities of a clinical geneticist. Particular emphasis is placed on follow-up, support, coordination of health surveillance and services to extended families. Family involvement is the essence of the service which geneticists provide.

- Laboratory Services for Genetics, Report of a working group to the NHS Executive and the Human Genetics Commission, 2000

The report recognizes the continuing role of laboratory genetics in service provision for single-gene disorders and recommends no immediate change to the current structure of the services, which are at present an integral part of the regional genetics centers and are often closely linked to university departments. However, it acknowledges that it is difficult to predict how laboratory services may need to evolve in the future if pharmacogenetic testing and testing for predisposition to common disease become a reality, and it recommends that the structure of the service should be kept under review for this reason. In assessing the effectiveness of current services, the working group found that the current regional basis for commissioning laboratory genetics services causes a number of problems, and recommends that the Department of Health should set up a national body to provide a "strategic steer" on the commissioning of these services. In collaboration with the devolved administrations in the other countries of the UK, the Department of Health should consolidate an UK-wide genetic testing network to ensure the best provision for testing for very rare genetic diseases. The working group will re-convene in two years' time to report on progress in implementing its recommendations.

-Genetics Commissioning Advisory Group, Department of Health, Genetic services: A guide for Primary care trusts, 2002 (http://www.doh.gov.uk/genetics/pctguide.doc)

-Cambridge Public Health Genetics Unit, Addressing Genetics, Delivering Health, A strategy for advancing the dissemination and application of genetics knowledge throughout our health professions, 2003 (http://www.phgu.org.uk/addressing_genetics.shtml)

'Key conclusions from the project include the need to: incorporate genetics into major clinical policy initiatives such as the National Service Frameworks; relate genetics education directly to clinical practice and current services; develop accessible, authoritative and up-to-date learning resources, for example on the web; involve patient groups in scoping what practitioners need to know; make genetics a compulsory, examinable part of curricula; and stress the place of genetics as part of an integrated clinical network. The report recommends the establishment of a national Steering Group for Genetics Education to provide a strategic overview, and of a national Centre for Genetics Education to coordinate programmes, develop and commission learning resources, and champion the place of genetics in health-professional education.'

IV- United States of America

Currently in the United States, genetic tests are regulated at the federal level through three mechanisms: 1) the Clinical Laboratory Improvement Amendments (CLIA); 2) the Federal Food, Drug, and Cosmetic Act; and 3) during investigation phases, regulations for the Protection of Human Subjects. Five organizations of the Department of Health and Human Services (DHHS) oversee genetic tests: the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Health Care Financing Administration (HCFA), the Office for Human Research Protections (OHRP), and the National Institutes of Health (NIH).

In addition to the Federal role, oversight of genetic tests is provided by states and private sector organizations. State health agencies, particularly state public health laboratories, have an oversight role in genetic testing, including the licensing of personnel and facilities that perform genetic tests. State public health laboratories and state-operated CLIA programs, which have been deemed equivalent to the Federal CLIA program, are responsible for quality assurance activities.

The private sector provides oversight in partnership with HCFA and the CDC by serving as agents for the government in accreditation activities. The private sector also develops laboratory and clinical guidelines and

standards. A number of professional organizations are involved in helping to ensure quality laboratory practices and in developing clinical practice guidelines to ensure the appropriate use of genetic tests. Professional organizations have also developed practice guidelines for specific disorders or groups of disorders (see *http://www.faseb.org/genetics/*).

- The Evaluation of Clinical Services Subcommittee, Great lakes Regional Genetic Group, Minimum Guidelines for the Delivery of Clinical Genetic Services, 1993

- American Society of Human Genetics & The American College of Medical Genetics, Report: Points to consider: ethical, legal and psychosocial implications of genetic testing in children and adolescents, 1995 (http://www.faseb.org/genetics/acmg/pol-menu.htm)
This report focuses on genetic testing in response to a family history of genetic disease or to parents' request for genetic testing. This report is grounded in several social concepts: First, the primary goal of genetic testing should be to promote the well being of the child. Second, the recognition that children are part of a network of family relationships supports an approach to potential conflicts that is not adversarial but, rather, emphasizes a deliberative process that seeks to promote the child's well-being within this context. Third, as children grow through successive stages of cognitive and moral development, parents and professionals should be attentive to the child's increasing interest and ability to participate in decisions about his or her own welfare. Counseling and communication with the child and family about genetic testing should include the following components: (1) assessment of the significance of the potential benefits and harms of the test, (2) determination of the decision-making capacity of the child, and (3) advocacy on behalf of the interests of the child.

- US National Society of Genetic Counselors, A position paper on Predisposition genetic testing for late-onset disorders in adults, 1997 (JAMA. 1997; 278: 1217-1220)
The Society recommends that professionals offering predisposition testing establish relationships with laboratories providing testing to optimize testing procedures and the clinical interpretation of test results. The Society does not take an explicit stance on commercial testing. The Society advocates responsible testing, whether commercial or noncommercial, for which persons receive appropriate education and counseling so that they can make autonomous informed decisions.

- National Institutes of Health - Department of Energy group working on the ethical, legal and social implication of human genome research, Report: Promoting safe and effective genetic testing in the United States, 1997 (http://www.nhgri.nih.gov/ELSI/TFGT_final/)
The National Institutes of Health created a Task Force in order to review genetic testing in the United States and, when necessary, to make recommendations to ensure the development of safe and effective genetic tests. The report of the Task Force showed problems affecting safety and effectiveness of genetic testing in the US such as: validity and utility of predictive tests, laboratory quality, and appropriate use by healthcare providers and consumers. On the basis of these findings, the Task Force made several recommendations to ensure safe and effective genetic testing. The Secretary of Health and Human Services followed up one recommendation by creating the Secretary's Advisory Committee on Genetic Testing (see below).

- Council of Regional Networks for Genetic Services, Guidelines for Clinical Genetic Services for the Public's Health, 1997 (http://www.cc.emory.edu/PEDIATRICS/corn/news/pubs.htm)
These guidelines provide a framework to develop a state genetic services system. Concerning general facility and operational requirements, the guidelines state that “the facility should be an identifiable unit in an accredited state or other medical school, a hospital, or a clinic accredited by the Joint Commission on Accreditation of Health Care Organizations. (…) Services should be available, accessible and culturally appropriate. (…) The center should develop and maintain an active program to monitor the quality of services provided. (…) Laboratories associated with the genetics unit should participate successfully in available proficiency testing programs. (…) No individual with a suspected genetic condition should be refused genetic services because of any disability or medical condition. State programs should provide support to those patients/families who are unable to pay”.

- *Statement. Professional disclosure of familial genetic information of the ASHG Social Issues Subcommittee on Familial Disclosure, 1998 (http://ns1.faseb.org/genetics/ashg/policy/pol-00.htm)*
This report focuses on the potential conflict within the health care professional-patient relationship when the patient refuses to warn at-risk relatives about relevant genetic information. Only exceptionally is a health care professional ethically permitted to breach confidentiality and as a legal matter ought to be privileged, that is, given a discretionary right to disclose genetic information to at-risk relatives without incurring liability provided certain conditions are met. Health care professionals should have an ethical duty to inform patients prior to testing as well as upon receipt of results that the information obtained may have familial implications.

- *American College of Medical Genetics, Standards and Guidelines for Clinical Genetics Laboratories, Second Edition, 1999 (http://www.faseb.org/genetics/acmg/stds/e.htm)*
These voluntary standards are an educational resource to assist medical geneticists in providing accurate and reliable diagnostic genetic laboratory testing consistent with currently available technology and procedures in the areas of clinical cytogenetics, biochemical genetics and molecular diagnostics. These standards establish minimal criteria for clinical genetics laboratories. The Standards should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. The accuracy and dependability of all procedures should be documented in each laboratory. This should include in-house validation and/or references to appropriate published literature. Specialized testing, not available to all laboratories, requires appropriate and sufficient documentation of effectiveness to justify its use. In determining the propriety of any specific procedure or test, the medical geneticist should apply his or her own professional judgment to the specific circumstances presented by the individual patient or specimen. Medical geneticists are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with these Standards. These Standards will be reviewed and updated periodically to assure their timeliness in this rapidly developing field.

- *Secretary's Advisory Commission on Genetic Testing, Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT, 2000 (http://www4.od.nih.gov/oba/sacgt.htm)*
SACGT has framed recommendations around the following five issues: 1) What criteria should be used to assess the benefits and risks of genetic tests? 2) How can the criteria for assessing the benefits and risks of genetic tests be used to differentiate categories of tests? What are the categories, and what kind of mechanism could be used to assign tests to the different categories? 3) What process should be used to collect, evaluate, and disseminate data on single tests or groups of tests in each category? 4) What are the options for oversight of genetic tests and the advantages and disadvantages of each option? And 5) What is an appropriate level of oversight for each category of genetic tests?

- *The Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) (http://www4.od.nih.gov/oba/sacghs.htm)*
This the successor of the Secretary's Advisory Committee on Genetic Testing (SACGT), chartered in September 2002, and set to expire in September 2004 unless otherwise renewed. "The committee's new charge is an expansion of the mission of the SACGT to more broadly consider the impact of genetic technologies on society. At the department's request, the committee may consider the broad range of human health and societal issues involving the development, use and potential misuse of genetic technologies and make recommendations as appropriate. The committee's charge includes considering the clinical, ethical, legal and societal implications of genetic testing and other technologies, and its members include experts in each of those areas, as well as consumer representatives."

Appendix 3: INTERNATIONAL FRAMEWORKS ON ORPHAN MEDICINAL PRODUCTS

As some medications that result from pharmacogenetic research may be eligible for an orphan medicine designation, the following are current regulations in this area.

I- European Organizations

- Regulation (EC) No. 141/2000 of the European Parliament and of the Council, on orphan medicinal products, 1999 (http://europa.eu.int/eur-lex/pri/en/oj/dat/2000/l_018/l_01820000122en00010005.pdf)

-Commission Regulation (EC) No. 847/2000, laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definition of the concepts 'similar medicinal product' and 'clinical superiority,' 2000 (http://europa.eu.int/eur-lex/pri/en/oj/dat/2000/l_103/l_10320000428en00050008.pdf)

-European Agency for the Evaluation of Medicinal Products, Committee for Orphan Medicinal Products; Points to consider on the calculation and reporting of the prevalence of a condition for orphan designation, COMP, London, 2002 (COMP/436/01) (http://www.emea.eu.int/pdfs/human/comp/043601.pdf)

- European Commission, Guideline on the format and contents of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another, Brussels, 2002 (ENTR/6283/00 Rev 1) (http://www.emea.eu.int/pdfs/human/comp/628300en.pdf)

II- European Countries

The below-listed member states offer the following incentive measures for orphan medicinal products; published within EMEA's Report on the first 3-year mandate of the Committee for Orphan Medicinal Products (COMP) April 2000-April 2003 (http://www.emea.eu.int/pdfs/human/comp/911803en.pdf)

Austria: offers fee waivers
Belgium: offers fee waivers
Denmark: offers fee waivers, and gives scientific advice to patients' organisations, researchers and industry
Finland: offers fee waivers, and gives advice on and funding of research
France: offers tax credits for research/industry, and gives funding of research and patients' organisations
Germany: gives rapid authorisation and reduced documentation for MAA, and funding of research
Greece: no incentives offered
Ireland: funding the (future) European Institute for Clinical Trials in Rare Diseases
Italy: gives funding to research, the National Center for Rare Diseases (Instituto Superiore di Sanità – ISS), Network of Public Health Insitiutions on Rare Diseases, National project on Rare Diseases, through the Ministry of Health, funds the National Registry for Rare Diseases, National Steering Committee for Rare Diseases
Luxembourg: no incentives offered
The Netherlands: offers fee waivers, offers tax credits for companies that utilize any type of high technological research
Portugal: offers fee waivers
Spain: offers fee waivers, and an accelerated marketing authorisation review
Sweden: offers fee waivers and scientific advice to sponsor, also fund National Database for Rare Diagnosis

United Kingdom: offers fee waivers, offers tax credits for research/industry [in the pharmaceutical industry (not specific for orphan medicines)], gives scientific advice to sponsors, rapid authorization, and a reduction in service charges for sponsors.

Contributions

This document was drafted by Angie Lanie, under the supervision of Ségolène Aymé. It was reviewed by the ESHG Public and Professional Policy Committee (PPPC). Members of the PPPC are:

- Ségolène Aymé (Paris, France), Chair
- Joerg Schmidtke (Hannover, Germany)
- Ulf Kristoffersson (Lund, Sweden)
- Jean-Jacques Cassiman (Leuven, Belgium)
- Shirley Hodgson (London, UK)
- Leo ten Kate (Amsterdam, The Netherlands)
- Violetta Anastasidou (Nicosia, Cyprus)
- Suzanne Braga (Bern, Switzerland)
- Domenico Coviello (Milan, Italy)
- Gerry Evers-Kiebooms (Leuven, Belgium)
- Helena Kääriäinen (Helsinki, Finland)
- Gyorgy Kosztolanyi (Pecs, Hungary)
- Jorge Sequeiros (Porto, Portugal)
- Lisbeth Tranebjaerg (Copenhagen, Denmark)

The document was also reviewed by members of the Institute for Prospective Technological Studies, which is a European Commission Joint Research Centre. Members include:

- Dolores Ibarreta (Sevilla, Spain)
- Emilio Rodriguez-Cerezo (Sevilla, Spain)

Drafts of this document were sent out to a wide range of individuals and organizations for consultation. The following consultants from 19 countries added critical comments by draft review, and/or at a pharmacogenetics workshop.

Austria
-Oskar A. Haas, Children's Cancer Research Institute, Vienna

Belgium
-Els Dequeker, Centre for Human Genetics, University of Leuven, Leuven
-Sofie Nørager, DG Information Society, European Commission, Brussels
-Erik Tambuyzer, Genzyme Corporation, Leuven

Czech Republic
-Milan Macek, Institute of Biology and Medical Genetics, 2nd School of Medicine, Charles University, Prague

Denmark
-Lisbeth Ehlert Knudsen, Institute of Public Health, University of Copenhagen, Copenhagen
-Claus Møldrup, Dept of Social Pharmacy, Royal Danish School of Pharmacy, Copenhagen

Finland
-Tarja Laitinen, GeneOS Ltd., Helsinki
-Ullamari Pesonen, Dept of Pharmacology and Clinical Pharmacology, University of Turku, Turku

France
-François Cambien, INSERM, Paris
-Mireille Claustres, Institut Universitaire de Recherche Clinique, Montpellier
-Francois Eisinger, CRLCC Institut Paoli-Calmettes, Marseille

-Evelyn Jacqz-Aigrain, Pharmacologie Pédiatrique et Pharmacogénétique, Hopital Robert Debré, Paris
-Kees Lucas, International Science and Technology Development, Biogen Idec

Germany
-Hans Peter Arnold, Business Development, EPIDAUROS Biotechnologie AG, Bernried
-Max Baur, Institute for Medical Biometry, Informatics and Epidemiology, University of Bonn, Bonn
-Angela Brand, ZiF, University of Bielefeld, Bielefeld
-Regine Kollek, Research Centre for Biotechnology, Society and the Environment, University of Hamburg, Hamburg
-Clemens Mueller, Department of Human Genetics, University of Wuerzburg, Wuerzburg
-Peter Propping, Institute of Human Genetics, University of Bonn, Bonn
-Achim Regenauer, Medicine and Genetic Technology, Münchener Rückversicherung, Munich
-Claus-Steffen Stürzebecher, Corporate Pharmacogenomics, Schering AG, Berlin

Greece
- Lina Florentin-Arar, AlfaLab Molecular Biology and Cytogenetics Center, Athens
-Achilleas Gravanis, Dept of Pharmacology, School of Medicine, University of Crete, Heraklion
-Emmanuel Kanavakis, Dept of Medical Genetics, Athens University, Athens

Hungary
-Lajos Botz, University of Pécs, Pécs
-György Fekete, Dept of Pediatrics, Semmelweis University, Budapest
-György Kosztolányi, University of Pécs, Pécs
-Janos Szolcsányi, University of Pécs, Pécs

Italy
-Pier Franco Pignatti, University of Verona

The Netherlands
-Henriette Roscam Abbing, Faculty of Law, University of Utrecht
-Han Brunner, Dept of Human Genetics, University Medical Center Nijmegen, Nijmegen
-Hans Scheffer, Dept of Human Genetics, University Medical Center Nijmegen, Nijmegen

Poland
-Michal Witt, Institute of Human Genetics, Poznan

Portugal
-António Amorim, IPATIMUP, University of Porto, Porto
-Isabel Marques Carreira, Cytogenetics Unit, University of Coimbra, Coimbra
-Catarina Resende de Oliveira, Depts of Biochemistry and Medical Biology, University of Coimbra, Coimbra
-Maria de Sousa, Institute for Molecular and Cell Biology, Porto
-Heloísa Gonçalves dos Santos, Medical Genetics Service of University Hospital S. Maria, Lisboa
-Orfeu Flores, STAB Vida, Oeiras
-João Lavinha, Instituto Nacional de Saúde, Lisboa
-Paula Pacheco, Human Genetics Centre, National Institute of Health, Lisboa
-Alexandre Quintanilha, IBMC, University of Porto, Porto
-Jorge Saraiva, Serviço de Genética Médica, Hospital Pediátrico de Coimbra, Coimbra
-Jorge Vieira, IBMC, University of Porto, Porto

Sweden
-Magnus Ingelman-Sundberg, Division of Molecular Toxicology, Karolinska Institute, Stockholm
-Ulf Landegren, Dept. of Genetics and Pathology/Molecular Medicine, Rudbeck Laboratory, Uppsala
-Jan Wahlström, Sahlgrenska University Hospital, Gothenburg University, Gothenburg

Switzerland
-Laurent Essioux, F. Hoffmann-La Roche Ltd, Basel
-Klaus Lindpaintner, Roche Genetics and Roche Center for Medical Genomics, Basel
-Detlef Niese, Clinical Development and Medical Affairs, Novartis Pharma AG, Basel

Turkey
-Meral Ozguc, Department of Medical Biology, Hacettepe University Faculty of Medicine, Ankara

United Kingdom
-Elizabeth Anionwu, Mary Seacole Centre for Nursing Practice, Thames Valley University, London
-Celia Brazell, Director Genetic Science & Technology, GlaxoSmithKline, Middlesex
-Kevin Cheeseman, Development, Pharmacogenetics, AstraZeneca R&D Charnwood, Leics
-Tara Clancy, NoWGEN, Dept. of Medical Genetics, St. Mary Hospital, Manchester
-Ann Daly, Pharmacogenetics Group, University of Newcastle Medical School, Newcastle upon Tyne
-David Goldstein, University College London, London
-Peter Harper, Institute of Medical Genetics, University of Wales College of Medicine, Cardiff
-Adam Hedgecoe, University of Sussex, Brighton
-James Jarrett, School of Medicine, Health Policy and Practice, University of East Anglia, Norwich
-Graham Lewis, Science and Technology Studies Unit, Dept of Sociology, University of York, York
-Theresa Marteau, Psychology and Genetics Research Group, Kings College London, London
-Duncan McHale, Clinical Pharmacogenomics, Sandwich Laboratories
-David Melzer, Institute of Public Health, University of Cambridge
-Lefkos T Middleton, Genetics Research, GlaxoSmithKline Research & Development, Middlesex
-Eileen Neilson, Royal Pharmaceutical Society of Great Britain, London
-Marisa Papaluca Amati, European Medicines Evaluation Agency, Sector Clinical Safety and Efficacy, London
-Paul Pharoah, Strangeways Research Laboratory, Cancer Research UK, Cambridge
Yvonne Smithies, Genetic Science & Technology, GlaxoSmithKline, Middlesex
-Sarah Wilson, CESAGen, Lancaster University, Lancaster
-Alan Wookey, Pharmacogenetics Advisor, Experimental Medicine, AstraZeneca

International
-Mary H.H. Ensom, Faculty of Pharmaceutical Sciences, Children's and Women's Health Centre of British Columbia, The University of British Columbia
-Glenn A. Miller, Genzyme Genetics, Westborough, Massachusetts
-Kathryn A. Phillips, School of Pharmacy and Institute for Health Policy Studies, University of California San Francisco
-Alan Roses, Genetics Research, GlaxoSmithKline, Research Triangle Park, North Carolina
-Mark A. Rothstein, Institute for Bioethics, Health Policy and Law, University of Louisville School of Medicine, Louisville, Kentucky
-Jai Shah, Canadian Institutes of Health Research, Ottawa, Ontario