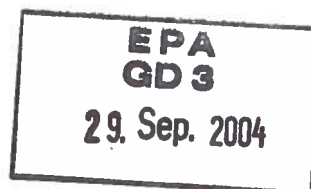


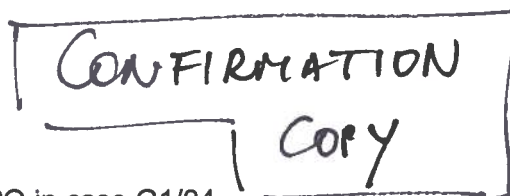
CENTRUM VOOR MENSELIJKE ERFELIJKHEID
CENTER FOR HUMAN GENETICS
CAMPUS GASTHUISBERG, O&N6
Herestraat 49
B-3000 LEUVEN



Fax: 00-49-89-23994465

22 pages total

OUR REFERENCE
YOUR REFERENCE
LEUVEN, 21 September 2004



To the Enlarged Board of Appeal of the EPO in case G1/04

Dear Mesdames, dear Sirs,

On August 31, 2004, we have submitted, on behalf of the Patenting and Licensing Committee of ESHG, a statement on G1/04.

Since that date, we have taken the time to elaborate on some of the arguments, and we have included additional comments in the text. May we kindly ask you to replace the earlier version by this second version, submitted hereby? Changes are in section 7 (page 8) and section 12 (page 12-13); they are underlined and indicated with a vertical line in the left margin. The conclusions are unchanged.

We realize that this submission comes after the deadline. However, we hope that it will hold up the procedures.

Sincerely,


Gert Matthijs

1. INTRODUCTION

This is in response to the call for submissions, Information from the EPO April 8, 2004 with respect to the case G 1/04. It is submitted in accordance with Art. 11b of the Rules of Procedure of the Enlarged Board of Appeal on behalf of the European Society of Human Genetics (ESHG) and relates especially to methods of diagnosis of genetic disorders (see accompanying cover letter).

ESHG welcomes the opportunity offered to it by the Enlarged Board of Appeal to comment on this important subject. We do not try to answer the questions which have been addressed to the Enlarged Board of Appeal (EBA) directly as we do not wish to assume the role of the Enlarged Board of Appeal. Instead we attempt a more general contribution from which we believe answers to these questions can be derived.

In the second and third annexes we provide references to some of the literature which has been studied, however we do not submit copies of these documents at this time. Time did not allow a full annotation of the comments below nor fuller reviews of supporting and diverging views expressed in the relevant literature. Should the Enlarged Board of Appeal require more detailed substantiation of certain points or copies of any of the articles, we would be pleased to prepare a more detailed analysis.

Please address all correspondence in this matter to:

Dr. Gert Matthijs,
Chair of the Patenting and Licensing Committee
Centre for Human Genetics
University of Leuven
Herestraat 49
B3000 Leuven
Belgium

Tel: 0032 16 346 070
Fax: 0032 16 346 060

2. THE NATURE OF HEREDITARY GENETIC DISEASES

Hereditary genetic diseases are caused by mutations in critical genes within the human genome. There are about 35,000 genes in the human genome and about 6,000 hereditary diseases have been listed. These diseases result in an evolutionary disadvantage which suppresses their incidence in the long term, i.e. after many generations. In equilibrium the rate of extinction of the underlying mutation from the gene pool is exactly matched by new spontaneous mutations. This equilibrium level is usually low and differs for each disease. Hence hereditary genetic diseases are generally rare diseases.

The healthcare systems of the member states of the EPC face the problem of the provision of diagnostic testing for this plethora of rare diseases rather than providing healthcare for only those few more frequent diagnostic methods that have a commercial incentive.

For a more detailed analysis see the annex to this paragraph.

3. DIAGNOSTIC TESTING METHODS BASED ON DNA ANALYSIS

The advent of PCR has greatly increased the possibilities for molecular diagnosis by mutation analysis, i.e. screening the DNA of a patient for mutations in the patient's DNA. PCR is used to amplify the region of interest (one or more exons at the genomic level or a fragment encompassing part of the coding sequence at the cDNA level). Several methods then exist to screen the amplicon for mutations (see e.g. Cotton et al. 2000). The gold standard is direct DNA sequencing because it allows one to identify the underlying mutation. It is however also one of the more expensive techniques (Sevilla et al. 2002). Other methods are used to identify the abnormal amplicons. They include established techniques like DGGE, SSCP, heteroduplex analysis, chemical and enzymatic mismatch detection, DHPLC and more recently, mass spectrometry. A plethora of other techniques and variations to these techniques are available. Most of these techniques are wide-spread, and easily accessible. Eventually, chip-based assays will replace some of these platforms.

For some rare diseases, like cystic fibrosis, diagnostic kits are on the market. For this disease, a limited number of mutations cover 80 to 95% of the diseases chromosomes, depending on the populations. Hence, kit-based assays are commonly in use.

The costs of developing a genetic test are very small, compared to the costs of developing a therapeutic. This has been shown by the fact that many public laboratories have been able to offer genetic tests within days or weeks after a gene was identified. Hence, the paradigm commonly expressed for therapeutics: No Patent – No Drug is not applicable to diagnostic testing.

Laboratories will initially use the published primer sequences and methods to set up the diagnostic method. However, very soon, the applications will vary, e.g. the technological platform, the primer sequences, the scope of the screening. Examples are common. Most European laboratories have introduced, and gradually improved, DHPLC as a platform for BRCA and other molecular testing (Wagner et al., 1999). In the case of Rett testing, it became soon apparent that several diagnostic laboratories had chosen different primer sets as compared to those originally published.

The application of diagnostic methods in laboratories worldwide has led to the improvement of these methods. This has been very well illustrated in the case of BRCA1 testing, where diagnostic centres have identified gene rearrangements and exonic deletions that were initially missed by the inventors of patent applications (Petrij-Bosch et al. 1997, Puget et al. 1999, Gad et al. 2002).

These applications are further improved as diagnostic laboratories and consortia of users of specific technological platforms work on quality standards for the mutation detection. An example has recently been given by DDQA, a consortium for the quality management of DHPLC. Similar initiatives will be taken for other technological platforms in the context of a European network on genetic testing, funded by the 6th Framework Programme of the EU.

4. THE SPECIFIC NATURE OF GENETIC DIAGNOSTIC METHODS

Genetic diseases are related to specific mutations of human DNA. To provide a good

diagnostic testing method, all possible mutations must be identifiable and the test must be of high quality, i.e. clinically and analytically validated. Due to the fact that the European population is a varied mixture of races, a good diagnostic testing method must check for any known mutation which has been identified anywhere in the world if the test is to be accurate and reliable.

To obtain all of the mutations which are linked to a gene, it is necessary that doctors and hospitals from all over Europe and in fact from all over the world contribute their knowledge about the mutations among their respective populations. The contributions to a good diagnostic test are worldwide, involving hundreds of doctors and health care providers. A debate is presently continuing at the highest level in Europe that where a communal effort of many individual persons is necessary for a technical advancement then the results of such communal efforts should not be patentable. The need to allow unfettered access to information and freedom to operate the diagnostic methods as well as the large number of persons involved in generating a reliable and accurate diagnostic test is undeniably applicable to genetic diagnostic testing. A European Network for genetic testing for rare diseases has been proposed ("Towards quality assurance and harmonisation of genetic testing services in the EU", ESTO, ed. D. Ibarreta et al. (Sept. 2003)). This report further emphasises the important issue that there can be a significant barrier to establishment of high quality standards in genetic testing if a private company is able to obtain a patent on a particular gene.

Also gene discovery, the precursor for a genetic test, is a community effort: examples are the Human Genome project, the BRCA Linkage Consortium (BCLC) and the BioBank in the UK. Based on the principles mentioned above, it has been accepted that the results of the Human Genome project should not be the subject matter of patents (cfr. Clinton and Blair statement).

The BCLC (<http://www.humgen.nl/lab-devilee/bclchome.htm>) was an international initiative to pool family sample materials and results from linkage analysis and other studies, founded in 1989, and was so successful that the location of the BRCA1 gene was eventually narrowed down with an exceptionally high LOD score of over 20 (a certainty with odds of 10^{20} to 1 – see Easton et al. 1999). From 1993 to 1998 it was supported by the Fourth Framework Biomed1 and Biomed2 programmes of the European Commission. At the end of it, the BCLC database held genetic data on over 700 breast cancer families from Europe, Canada, and USA. The number of centres involved in the BCLC was nearly 100. Allowing patent protection to only one organisation places the supportive work of the remaining 99 in question. Why contribute to one's own exclusion?

The UK BioBank (<http://www.ukbiobank.ac.uk/>) aims to obtain comprehensive data on the combined effects of genotype, life style and environmental exposure to assess the risk of developing the common multi-factorial diseases of later life, and involves the cooperation of some 500,000 men and women and £45 million of initial funding by the Department of Health, the Wellcome Trust and the Medical Research Council.

Hence it should be a goal of the EPC to prevent the patenting of genetic diagnostic test methods whose success typically depends on a large-scale, communal effort and where patenting could injure and influence in a negative manner the preparedness of doctors throughout the world to cooperate.

5. COMMERCIAL EXPLOITATION OF DIAGNOSTICS OF HEREDITARY GENETIC DISEASES

Genetic diagnostic testing in Europe is performed in the public health context, with few exceptions. It is estimated that around 735,000 genetic diagnostic reports are made per year in Europe. The mean cost is euro 573 per report (see Ibarreta et al above). There are 715 laboratories in Europe performing genetic tests. Of these 85% are affiliated to public hospitals or universities or other non-profit organisations. 15% are commercial. The average number of test per laboratory is low. Genetic tests are available for between 600 and 900 different diseases. Several international databases of genetic testing resources have been established, and they are available on-line (Aymé, 2000).

In the UK, genetic testing is offered by genetic laboratories that operate within the context of the National Health Services (NHS). Early in 2003, a Genetic Testing Network has been created to provide high quality, equitable laboratory services for patients and their families who require genetic advice, diagnosis and management. Also since 2003, the Department of Health (DH) has supported 2 National Genetic Reference Laboratories and 6 Genetic Knowledge Parks (Two National Genetics Reference Laboratories in Salisbury and Manchester, specialising in assessing and developing new genetic tests and technologies for the benefit of patients - each receiving £500,000 funding a year- and Genetics Knowledge Parks in Oxford, Cambridge, London, the North West and Newcastle).
(<http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Genetics/GeneticsGeneralInformation/fs/en>)

Finally, a Rare Disease Service has been installed in April 2003 to offer a mechanism for confirmation and testing for mutations identified by research laboratories (<http://www.ngri.org.uk/Manchester/Pages/NGRLLrarehome.htm>). In this way, patients and families with extremely rare conditions will have access to molecular genetic testing and prenatal diagnosis.

These are in line with the policy of the UK government on genetics, set out in the White Paper (June 23, 2003)
(http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Genetics/GeneticsGeneralInformation/GeneticsGeneralArticle/fs/en?CONTENT_ID=4016430&ch=RnGBgL).

In countries like Belgium and the Netherlands, the genetic testing is offered by a limited number of recognised (*by law*) centres for human genetics. The reimbursement system is very flexible in these countries: the genetic conditions to which reimbursement applies are not specified in law; as a result, any genetic test will be reimbursement by the health insurance.

In France, only a few genetic tests have been included in the nomenclature for reimbursement. All other tests are offered by laboratories that have either a scientific interest in the disease or are part of larger diagnostic centres that can support in depth testing or testing for rare conditions. The French Ministère de la Santé, de la Famille et des Personnes Handicapées has recently granted specific funds to support these activities to a selection of expert diagnostic laboratories (for cystic fibrosis, for cancer genetics and for neuromuscular testing, a total budget of several millions of euros has

been granted over the past 3 years).

(<http://www.sante.gouv.fr/adm/dagpb/bo/2001/01-44/a0442896.htm>;

<http://www.sante.gouv.fr/adm/dagpb/bo/2003/03-24/a0241668.htm>;

<http://www.sante.gouv.fr/adm/dagpb/bo/2003/03-24/a0241669.htm>)

As a practical result, tests are available for a plethora of genetic conditions in these countries.

Gradually, these expert laboratories will organise themselves into international networks where diagnostics are offered for the very rare conditions under quality rules. This will require the medical geneticists to be in close contact with the referring physician.

Case studies:

Several companies have marketed CFTR kits. A kit should be distinguished from a diagnostic method. The kit is the hardware used in a diagnostic method. For cystic fibrosis they have been on the market relatively soon after the gene was cloned. Thanks to the competition between these companies, these kits have constantly been improved, and most of the laboratories in the world are using them. Thus, it is good indeed if companies step into the diagnostic kit market.

The owner of the US patent on hemochromatosis uses a very rigid licensing policy (Merz et al. 2002). As a result, several companies have refrained from developing kits for this disease. The cost remains high, or the public laboratories use mainly home-brew kits.

Two examples of companies that capitalize on (monopolies on) gene patents are Myriad and Athena Diagnostics. It is true that this has allowed e.g. Athena to offer comprehensive and fast testing for PKD or TSC. The drawback is that the costs are exceedingly high, because competition cannot rule the market.

Generally, the low numbers of reports per disease results in the need by commercial companies to use the patent system to prevent third parties from testing in order to get a reasonable number of tests concentrated in one location. This location maybe outside the member states of the EPC. The attempt to make a commercial success out of genetic testing results in an overly profit-oriented and restrictive behaviour.

6. ART. 52(4) EPC, ETHICS AND INDUSTRIAL APPLICABILITY

Art. 52(4) EPC refers to industrial applicability. However, the exception for methods of surgery, therapy and for diagnostic methods is said to be derived from ethical principles. The ethical dimension is of particular importance in genetic testing due to the fact that the results of such a test impact not only individuals but also the family related to the individuals, the work place, insurance, etc.

In the decision T 0024/91, the Board stated:

2.4 It is generally accepted that the exclusions from patentability under Article 52(4) EPC are based on socio-ethical and public health considerations. The intention underlying this article is to ensure that nobody who wants to use the methods

specified in this article as part of the medical treatment of humans or animals should be prevented from this by patents.

One can elicit from this statement that the purpose of the provision is to prevent patents being used for certain methods used in the treatment of humans or animals. No mention is made of doctors.

In T385/86 the following can be found:

3.1.....

Moreover, in the "Grounds given with regard to the ratification of international patent conventions" it is stated that the exclusion made by Article 52(4) EPC is in line with existing case law and literature and was ethically motivated.....

This statement points to ethical considerations as being relevant. The revision of the EPC has kept the wording of Art. 52(4) EPC emphasising the importance of this provision despite attempts to remove it and also placed the wording alongside those provisions dealing with matters of morality such as *ordre public*. This latter move reinforces the ethical motivation as the basis for Art. 52(4) EPC.

However in the decision G5/85 the Enlarged Board of Appeal stated:

22. The intention of Article 52(4) EPC, again as recognised by the Federal Court of Justice, is only to free from restraint non-commercial and non-industrial medical and veterinary activities.

This statement is confusing, particularly the word “non-commercial”. Healthcare is generally a commercial activity. So it is not clear what non-commercial means in this context. Further although reference is made to “non-industrial activities” the suggestion or implication is that there would be (or might be) some industrial medical and veterinary activities. No definition is given of where the boundary would be between these two types of activities – assuming that both exist and there is a boundary. Summarising, this statement points to the question of industrial activity without reference to ethics while not providing a clear teaching as to how it should be applied.

The confusion which surrounds this subject is well documented in the legal discussion printed in OJ EPO, vol. 5, 2004, pp 229 to 269.

In order to find a way out of this confusion, it appears necessary to investigate the motivation behind Art. 52(4) EPC more carefully.

7. RELATIONSHIP BETWEEN ART. 52(4)EPC AND ETHICS AND INDUSTRIAL APPLICABILITY

There is considerable support for the view that Art. 52(4) EPC is a true exception to patentability (examples: Benkard, EPÜ, Art. 52, Rdn 227, 228; Singer/Stauder 3rd Ed., Art. 52, 61, 62; Paterson, 2nd Ed. 9-36; Schulte, 6th Ed. §5, Art. 52(4) u Art. 57 EPÜ, Rdn 17).

That is:

despite the subject matter being potentially patentable from a technical point of view,
and

despite investment being necessary for such methods and there being an argument that
this investment should be protected by a monopoly right, and

even if the method involved is industrially applicable,

such methods are not to be the subject matter of patents.

Thus the regulator selected a fiction for the invalidity of these claims, lack of
industrial applicability appeared to be the most reasonable one to select of the three
specified in Art. 52(1) EPC.

Further there is significant support for the view that at least part of a motivation for
Art. 52(4) EPC is ethical, even if reference is made to the lack of industrial
applicability in the provision.

We propose the following as a summary of the motivation for Art. 52(4) EPC:

**from ethical considerations, the living human and animal body is generally not a
suitable substrate for an industrial process.**

We submit that this ethical principle would find general acceptance among right-
thinking persons in the member states of the EPC. Further this principle links ethical
principles to industrial applicability in an elegant and satisfying way thus eliminating
some of the confusion if these two aspects are considered separately.

A further accepted view is:

**the work of a doctor or other type of medical practitioner including a medical
geneticist is not an industry but a profession and is therefore not industrially
applicable. Methods which intrude too severely in the doctor-patient
relationship are excluded from patenting.**

We are not convinced that it is correct to examine methods touching on the doctor-
patient relationship under Art. 52(4) EPC. This relationship is devoid of industrial
applicability as it is a professional one, i.e. it appears that it should be dealt with under
Art. 57 EPC. So the examination of claims to methods of diagnosis must include
consideration of both Art. 52(4) EPC and Art. 57 EPC separately.

A further view expressed in T0385/86 which should be retained is that
(notwithstanding other reasons for lack of patentability):

**diagnostic methods to be excluded from patent protection are also those whose
results immediately make it possible to decide on a particular course of medical
treatment.**

Finally, in line with other decided cases on surgery and therapy:

a single step which contravenes Art 52(4) EPC is sufficient to render a claim invalid.

The case law of the EPO Appeal Boards is rather consistent on this last point as far as surgery and therapy is concerned and there appears to be no legally acceptable reason why the different elements of Art. 52(4) should be applied in a differentiated manner. There is no basis in Art. 52(4) EPC for such a differentiated approach.

A basis for this rule can be found in the need to free non-industrial medical and veterinary activities from patent rights and in that doctors are to be free at all times to take actions they consider suited to cure illness or to diagnose them by means of investigative methods (OJ EPO, 5/2004, page 231, last paragraph, citing G5/83, Schulte). In providing protection for such activities it is necessary to consider both direct and indirect or contributory infringement. Indirect infringement is based on conspiracy – a combined act in the knowledge of what you do (rather than being an innocent bystander). The requirement for indirect infringement is substantive contribution and knowledge of what is being done. It is assumed that a doctor or a medical geneticist will be fully aware of the circumstances and the reasons for his or her services. Further in a diagnostic method a doctor or medical geneticist will provide a valuable contribution to the overall method of diagnosis, e.g. the medical geneticist will provide the analysis which decides whether a new and unknown mutation of a gene is pathogenic or not.

Indirect infringement can be founded on a single method step carried out by a doctor or medical geneticist in combination with other persons, hence the need to free non-industrial medical and veterinary activities from patent rights where only a single “doctor step” is performed.

8. THE NATURE OF ETHICAL ARGUMENTS AS APPLIED IN LAW

One of the difficulties of applying ethical principles to law, is that as soon as ethical principles are formulated it is possible to imagine situations in which the ethical code should be broken. Hence ethical principles are not suitable for the day-to-day legal decision making.

Ethical principles must be concretised in language which can then provide a more secure basis for decision. We come, therefore, to the conclusion that the wording of Art. 52(4) EPC is the concretisation of the general ethical principle that the living human and animal body is not a suitable substrate for an industrial process. The wording has limited the application of this principle to certain types of processes applied to the human body. By limiting the application of the ethical principle severely, it can be hoped that the number of situations where the application of the rule is unjust is reduced to a minimum. The provision has been maintained in the revision of the EPC despite attempts to remove it. One can conclude from this that the provision is therefore sufficiently just as to find general approval.

It should be understood that Art. 52(4) EPC makes it clear (by reference to the human or animal body) that even if patients in a hospital are transported by conveyor belts, even if the nurses, doctors and surgeons are robots, and even if from start to finish of the healthcare is controlled remotely using software copied from the automotive

industry, that such a hospital would not be a factory and the healthcare would not be an industry and the methods applied to the patients would not be industrial processes. The question addressed by Art. 52(4) EPC is not the technical nature of the methods used, not the investment in such methods which might benefit from protection by a monopoly right nor that healthcare is a commercial activity involving reimbursement nor whether the method is industrially applicable but rather that the living human or animal body should not be treated as a substrate for an industrial process.

There appears to be some confusion on this point. Some try to find how a particular method can be applied industrially and if they can find such an implementation conclude that such a method is not excluded by Art. 52(4) EPC. Such an analysis is incorrect. The investigation of industrial applicability belongs to Art. 57 EPC alone. Art. 57 and Art. 52(4) EPC are separate provisions – a method of diagnosis must be examined under both these heads separately.

9. WHAT IS A STEP IN A DIAGNOSTIC METHOD AS APPLIED TO THE HUMAN OR ANIMAL BODY?

Well known and accepted steps in a diagnosis are:

Visual examination of the eye, throat, skin, etc. No tactile or audio contact is necessary in every case.

Tactile examination of the limbs, abdomen, etc. No visual or audio contact is necessary in every case.

Audio examination of the body, e.g. use of a stethoscope, listening to a cough, question and answer of taking a patient's history, possibly including a family history. No tactile or visual contact is necessary in every case.

We propose the view that each and any such diagnostic method step is to be understood as applied to the human body.

Summarising the above, a step in a diagnostic test as applied to the human or animal body (and therefore excluded from patentability) is:

Any explicit or implicit audio, visual or tactile contact with the patient which is a substantive act in the method of diagnosis.

By substantive is meant that it contributes to the final diagnostic result. For example, printing the form for informed consent may be done using a patented method. However, the printing itself does not contribute to the diagnostic result. The Appeal Board in T385/86 said something similar: "implicitly contains information which is of use in making a diagnosis".

It is not necessary that all steps of the diagnostic method need to be applied to the human or animal body. One such step is sufficient.

10. OUTCOMES OF APPLICATION OF ART. 52(4)

In order to develop the argument further it is useful to take a generalised claim to a method of diagnosis which involves testing of a patient's DNA.

Take the following claim as an example:

A method of diagnosing a malady of a human patient comprising the steps of:

- 1) removing a tissue sample from the human patient,
- 2) ex vivo analysis of the tissue sample
- 3) determining an alteration in the sequence of a human gene
- 4) determination that the alteration being predisposing for the malady
- 5) communicating the result to the patient.

Step 1 is a surgical or other step applied to the patient. Such a step would render a claim invalid in accordance with Art. 52(4) EPC. It is a tactile contact with the patient which is a substantive act in the diagnostic method.

Step 5 is a step involving the patient. It requires an audio, visual or a tactile contact with the patient which is a substantive act in the diagnostic method. Hence the presence of such a step would make the claim invalid.

11. INFORMED CONSENT IN EUROPE

Steps 2 and 3 relate to an analysis which is normally carried out in the laboratory. There is wide support for the patentability of in vitro test methods.

However, in the case of step 3, in genetic testing it is submitted that there is an implicit step of patient consent for the testing of patient DNA. Step 3 cannot be contemplated without patient consent. This consent is an audio, visual (or even tactile) contact with the patient which is a substantive act in the method of diagnosis. Such a request for consent involves patient contact in the same manner as other well known diagnostic method steps, e.g. taking a patient history. Hence a claim containing such a step is invalid as this taking of the consent has been implicitly practised on the human body.

As justification for an implied or actual consent step the following arguments are submitted.

The French law requests informed written consent (Art.16-10). « Le consentement exprès de la personne doit être recueilli par écrit préalablement à la réalisation de l'examen, après qu'elle a été dûment informée de sa nature et de sa finalité. Le consentement mentionne la finalité de l'examen. »

The French law also considered the fact that the result of an analysis will impact the entire family. « En cas de diagnostic d'une anomalie génétique grave posé lors de l'examen des caractéristiques génétiques d'une personne, le médecin informe la personne ou son représentant légal de la responsabilité qui serait la leur s'ils ne prévenaient pas les membres de la famille potentiellement concernés dès lors que des mesures de prévention ou de soins peuvent être proposées à ceux-ci. L'information

communiquée est résumée dans un document signé et remis par le médecin à la personne concernée, qui atteste de cette remise. ... »

Art. L.1131-3 of the same code specifies : « Sont seuls habilités à procéder à la réalisation des examens des caractéristiques génétiques d'une personne ou de son identification par empreintes génétiques à des fins médicales les praticiens agréés à cet effet par l'Agence de la biomédecine mentionnée à l'article L.1418-1... ».

Hence, the completion of the genetic test is reserved to medical practitioners.

Although the above is a French law is a separate implementation on bioethics, we submit that it is a specific implementation subsequent to the European Directive 95/46/EC, OJ 1995 No. L281/31, and therefore applicable to the whole of Europe. Following Graeme Laurie, in "Genetic Privacy", Cambridge University Press, 2002, personal health data, including genetic data are clearly caught by the provisions of this directive. Indeed, they qualify as "sensitive personal data" and, as such, receive more stringent protection, permitting processing in only limited circumstances of which one is explicit consent of the patient.

In the UK, the Joint Committee on Medical Genetics of the Royal College of Physicians, Royal College of Pathologists and British Society for Human Genetics has drafted a document on 'Consent and confidentiality in genetic practice'. It proposes that « Consent should be obtained prior to a test with genetic implications being performed. [...] consent should have been obtained before medical genetic information is disclosed. »

The general guidelines of the Department of Health place the onus for consent with the clinician obtaining the genetic information or the sample. In the specific context of genetics, it is considered good practice to confirm that the sharing of information with other family members is acceptable to the individual being seen and to document this. Patients may indicate their informed consent either orally or in writing. But in the case of predictive genetic testing, it is important that a written record is available of the patient's consent and other wishes.

A test result is an integral part of the medical genetic information that will be given to consultands or probands upon consultation.

In a 'Review of ethical issues in medical genetics' (2001), consultants to the World Health Organisation (WHO) have noted that 'screening (with the exception of mandatory newborn screening), diagnostic genetic testing, prenatal diagnosis, treatment and research should be preceded by informed consent. Informed consent means that the person understands the risks, discomfort, and benefits of the procedure(s). Formal informed consent, in the form of a written document, is not necessary for procedures that constitute part of routine care. [...]. All persons having genetic screening or testing, however, including the parents of newborns, should be informed before testing about the major characteristics of the disorder(s) screened or tested for [...].

ESHG has previously recommended in "Provisions of genetic services in Europe: current practices and issues", (European Journal of Human Genetics (2003) vol. 11, suppl. 2) that the provision of genetic services should be based on respect of principle

of self-determination of the persons concerned and that for this reason genetic testing, even when offered systematically should be subject to express, free and informed consent. This view has also been supported in the draft Fiori report (29 August 2001) for the European Parliament concerning the social, legal, ethical and economic implications of human genetics.

It is requested that the Enlarged Board make a general statement that diagnostic method like step 2 is invalid due to an explicit or implicit audio, visual or tactile contact with the patient for the purpose of informed consent which therefore renders the method step to be practiced on the human body.

Or:

The Enlarged Board indicate in their opinion that where the laws of a country specify that informed consent is required before DNA testing can be carried out, then a step like step 2 would be invalid because of an explicit or implicit audio, visual or tactile contact with the patient for the purposes of informed consent.

In addition step 4 is a critical step. In genetic testing this involves

- a) comparison of the determined sequence with known mutations or a similar method or
- b) requires an intervention by a medical geneticist if the mutation which has been found is not known. The intervention by a medical geneticist is a step involving a professional whose activity is not industrially applicable, i.e. is excluded by Art. 52(4) and/or Art. 57 EPC.

In addition, if the claimed process immediately results in a final diagnosis then the claim is not patentable. For instance, the detection of an expansion in the CAG-repeat in the huntingtin gene in a consultand from a family in which Huntington's disease is known to occur, immediately implicates that this person will develop the disease. The diagnosis is complete as soon as the results of the genetic test are known. Similarly, the identification of a truncating mutation in the BRCA1 or BRCA2 gene confirms the predisposition to breast and ovary cancer in the consultand.

12. RELEVANCE OF T385/86 AND T0964/99

T385/86 has been criticised by R. Moufang in "Methods of medical treatment under patent law", 24 IIC, no. 1, 1993, 18-49, at 46 and 47, as effectively reducing the practical application of Art. 52(4) EPC to zero as far as diagnostic tests are concerned. T385/86 appears to be examining Art. 57 rather than Art. 52(4) EPC in that it discusses the relationship between doctors and their patients. T0964/99 appears to have the better legal basis of the two decisions and a clearer understanding and interpretation of Art. 52(4) EPC.

One issue that is of importance is the case where there is both an industrial and a non-industrial implementation of claimed subject matter. For example, in general or very often there is always a private and non-commercial way of implementing a method. Where there is both a commercial and a private and non-commercial use, the latter is excluded from infringement by the national laws of the member states of the EPC. Hence there is no need to add to each method claims the words "excluding private

use". This type of use is excluded from infringement by force of national law. Only in the case that exclusively private uses can be contemplated for a method, has the EPO seen the need to concern itself with the exclusion provided by Art. 57 EPC (a good example is given in T 0074/93, OJ EPO 1995 page 712).

However, no such general exclusion from infringement exists for medical and veterinary activities, in particular because they involve reimbursement and are therefore in some way "commercial" and not "private and non-commercial". As stated in G5/83, Art. 52 (4) and Art. 57 EPC must be interpreted and applied in such a way that non-industrial medical and veterinary activities are freed from patent rights. Contrary to the situation with private and non-commercial use which is excluded from infringement by national law, this means that there must be explicit wording in the patent claims which excludes a use covering non-industrial medical and veterinary activities.

Accordingly, either the claim language must be modified to remove any step that would be carried out by a doctor or a medical geneticist, or the claim must contain a disclaimer to this effect. In the case of mixed industrial and non-industrial uses, the same rules apply as have been detailed above. All method steps must be removed which would render that part of the claim invalid (i.e. that part relating to the non-industrial application) or there must be positive recitation in the claim that limits the scope of protection to exclude such a use or a disclaimer must be added to the claim.

13. CONCLUSIONS

The following rules are proposed:

1. From ethical considerations, the living human and animal body is generally not a suitable substrate for an industrial process.
2. The work of a doctor or other type of medical practitioner including a medical geneticist is not an industry but a profession and is therefore not industrially applicable. Methods which intrude too severely in the doctor-patient relationship are excluded from patenting (Art. 57 EPC).
3. Diagnostic methods to be excluded from patent protection are also those whose results immediately make it possible to decide on a particular course of medical treatment.
4. A single step which contravenes Art 52(4) EPC is sufficient to render a claim invalid.
5. Any claim which includes an explicit or implicit audio, visual or tactile contact with the patient which is a substantive act in the method of diagnosis is excluded from patentability (Art. 52(4) EPC).
6. Any step which requires the testing of DNA of a human requires explicitly or implicitly a step of patient contact to obtain consent.

We request the opportunity to present the above arguments before the Enlarged Board of Appeal in an oral hearing.

Annex 1 to the nature of hereditary genetic diseases

The genetic makeup of a population changes over time as new alleles arise by mutation or are introduced by immigration, and as rare, pre-existing alleles disappear when all individuals carrying them leave the population or die. Changes in the frequency of alleles within the population are the basis for evolution.

The incidence of genetic diseases, such as cystic fibrosis, thalassemia or familial breast and ovarian cancer that are determined by a single gene, is determined by the variation in nature and number of the disease-causing alleles. The Hardy-Weinberg law is used to understand allele, genotype and phenotype frequencies of single-gene traits in a genetically stable population and while models beyond Hardy-Weinberg take into account features like genetic drift, new mutations, heterozygous advantage and natural selection.

In the simplest model of a population at Hardy-Weinberg equilibrium, allele frequencies do not change from generation to generation. In such a population, the genotype frequencies of p^2 , $2pq$ and q^2 are achieved in just one generation and maintained in subsequent generations. Consider a recessive disease like PKU. The frequency of the disease is roughly 1 in 3600 in most European populations. Or, each couple has a risk of 1 in 3600 of having a child with PKU at each pregnancy. From the frequency of the disease (q^2), the frequency of the disease allele (q) can be derived: $1/60$. On the basis of the Hardy-Weinberg equation ($p^2 + 2pq + q^2 = 1$), it is calculated that roughly 1 in 30 people ($2pq$) are heterozygous carriers of the disease.

In natural populations however, conditions almost always deviate from the Hardy-Weinberg equilibrium: some populations are not very large, individuals do not always mate at random, new mutations do arise, there is migration into and out of the population, and different genotypes do generate differences in survival rates.

If the genotype affects the probability of survival and reproduction – which it does in the case of many congenital diseases – the genotype frequencies of the real population will change as their individual members will mature from zygote to adults. Fitness is an individual's relative ability to survive and transmit its genes to the next generation. Differences in fitness will thus have a profound effect on the allele frequencies. As the allele frequency diminishes, individuals homozygous for the disease allele are very rare because most of the recessive disease alleles occur in heterozygotes, which do not experience negative selection. For lethal recessive diseases, the frequency of the disease allele will thus only slowly decrease over time, moving closer and closer to a value of zero.

The reality is that many recessive genetic diseases persist in the human populations at low but stable frequencies. Heterozygous advantage is one phenomenon that maintains recessive disease alleles in a population: the heterozygotes have a higher fitness than either homozygote. Sickle cell anaemia is a lethal disease for which the high carrier frequency is a result of resistance to malaria. The relatively high frequency of cystic fibrosis, hemochromatosis and possibly other diseases may also be due to this phenomenon.

Dominant diseases do not disappear because the loss of alleles from the gene pool is constantly restored by the occurrence of new mutations. The susceptibility of the gene

to such mutations will determine its frequency. The neurofibromatosis type I gene and the achondroplasia gene are examples of genes that show a relatively high rate of de novo mutation. Also, in some lethal X-linked diseases, like Duchenne Muscular Dystrophy, the de novo mutation rate is very high.

Thus, the present day frequencies of the different diseases (see table 1) are the result of a combination of such phenomena.

The natural frequency of new point mutations varies widely between genes, but averages about one event in any specific gene per 500,000 zygotes. This estimate is based on the frequency of dominant diseases in families with no prior cases. Almost all point mutations arise in sperm (rather than in oocytes), each containing around 35.000 genes. There are therefore about 35.000 mutations per 500,000 sperm, so one expects 7.5 % of viable sperm (and babies) to carry a new genetic mutation. Of course, only a minority of these occur within genes that produce clinically significant effects in a dominant way. The other add to the frequency of recessive conditions, or to polymorphic variation in the population.

Table of frequencies of genetic disorders in the EP population.

Disease	Incidence
Recessive diseases	
Thalassemia	1/10 in parts of Italy, 1/50-100 in other circum-Mediterranean populations
Sickle-cell anemia	1/625 African-Americans, up to 1/50 in central Africa
Cystic fibrosis	1/1,800-2,500 Caucasians
Tay-Sachs disease	1/300.000; 1/3,000 Eastern European Jews
Phenylketonuria (PKU)	1/10,000 Caucasians, 1/5,000 in Irish, Scottish populations and Yemenite Jews, 1/30,000 in Sweden and 1/2,600 Turks, 1/119,000 in Japan
Albinism	1/10,000 in Northern Ireland
Canavan disease	1/6,400 Ashkenazi Jews
Galactokinase deficiency	1/2,200,000 in Switzerland, 1/157,000 in Germany, 1/52,000 in all gypsies, 1/1,600-2,500 in Vlax Roma.
Spinal Muscular Atrophy	1/10,000 in most populations
Hemochromatosis	1/400 Caucasians are homozygous, approximately 1/1,000 to 1/2,000 are affected.
Dominant diseases	
Achondroplasia	1/10,000-30,000, of which seven-eighths are <i>de novo</i>
Hypercholesterolemia	1/500, 1/122 French Canadians
Huntington disease	1/25,000 Caucasians
Adenomatous polyposis coli	1/6,000
Hereditary nonpolyposis colon cancer	Up to 1/200
Neurofibromatosis type I	1/3,000-5,000
Osteogenesis imperfecta	1/5,000-10,000
Retinoblastoma	1/20,000
X-linked diseases	
Hemophilia A	1/10,000
Fragile X syndrome	1/3,500-4,000 males, 1/8,000 females
Duchenne Muscular Dystrophy	1/3,500 in all populations

Chromosomal abnormalities

Down syndrome	1/700 to 1/1,000
Klinefelter syndrome	1/1,000 males
Turner syndrome	1/2,500 to 1/10,000 females

Case study:

In Mediterranean populations, like for instance in Sardinia, the incidence of thalassemia has been reduced to virtually zero in the 80's and 90's, thanks to a governmental screening program. For example, fall of birth rate of babies with homozygous beta-thalassemia dropped fifty-fold in the period 1976 to 1990. The success is due to technology for carrier screening and prenatal diagnosis being made widely available, and most carriers were identified prenuptially. The major challenges are good public education and counselling at the community level. No private, e.g. industrial partners were necessary or present in this achievement.

The above confirms that genetic screening involves a community action, in which diagnostic testing and the free flow of information go hand in hand. The public health services have been dealing with this relatively adequately in most instances. However, such a strategy requires freedom to operate the diagnostic method within a communal context and the motivation to exchange information freely.

Annex 2 cited references

Wagner T, Stoppa-Lyonnet D, Fleischmann E, Muhr D, Pages S, Sandberg T, Caux V, Moeslinger R, Langbauer G, Borg A, Oefner P.

Denaturing high-performance liquid chromatography detects reliably BRCA1 and BRCA2 mutations. *Genomics*. 1999;62:369-76.

Sevilla C, Julian-Reynier C, Eisinger F, Stoppa-Lyonnet D, Bressac-de Paillerets B, Sobol H, Moatti JP. Impact of gene patents on the cost-effective delivery of care: the case of BRCA1 genetic testing. *Int J Technol Assess Health Care*. 2003;19:287-300.

Gad S, Caux-Moncoutier V, Pages-Berhouet S, Gauthier-Villars M, Coupier I, Pujol P, Frenay M, Gilbert B, Maugard C, Bignon YJ, Chevrier A, Rossi A, Fricker JP, Nguyen TD, Demange L, Aurias A, Bensimon A, Stoppa-Lyonnet D. Significant contribution of large BRCA1 gene rearrangements in 120 French breast and ovarian cancer families. *Oncogene*. 2002 ;21:6841-7.

Sevilla C, Moatti JP, Julian-Reynier C, Eisinger F, Stoppa-Lyonnet D, Bressac-de Paillerets B, Sobol H. Testing for BRCA1 mutations: a cost-effectiveness analysis. *Eur J Hum Genet*. 2002 ;10:599-606.

Gad S, Scheuner MT, Pages-Berhouet S, Caux-Moncoutier V, Bensimon A, Aurias A, Pinto M, Stoppa-Lyonnet D. Identification of a large rearrangement of the BRCA1 gene using colour bar code on combed DNA in an American breast/ovarian cancer family previously studied by direct sequencing. *J Med Genet*. 2001;38:388-92.

Puget N, Stoppa-Lyonnet D, Sinilnikova OM, Pages S, Lynch HT, Lenoir GM, Mazoyer S. Screening for germ-line rearrangements and regulatory mutations in BRCA1 led to the identification of four new deletions. *Cancer Res*. 1999 ;59:455-61.

Petrij-Bosch A, Peelen T, van Vliet M, van Eijk R, Olmer R, Drusedau M, Hogervorst FB, Hageman S, Arts PJ, Ligtenberg MJ, Meijers-Heijboer H, Klijn JG, Vasen HF, Cornelisse CJ, van 't Veer LJ, Bakker E, van Ommen GJ, Devilee P. BRCA1 genomic deletions are major founder mutations in Dutch breast cancer patients. *Nat Genet*. 1997;17:341-5.

Easton DF, Bishop DT, Ford D, Crockford GP. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. The Breast Cancer Linkage Consortium. *Am J Hum Genet*. 1993;52:678-701.

Merz JF, Kriss AG, Leonard DG, Cho MK. Diagnostic testing fails the test. *Nature*. 2002 7;415(6872):577-9.

Nuffield Council of Bioethics. Discussion Paper, The ethics of patenting DNA, published 23 July, 2002 (<http://www.nuffieldbioethics.org/patentingdna/index.asp>).

European Society of Human Genetics. Provision of genetic services in Europe: current practices and issues. *Eur J Hum Genet*. 2003;11 Suppl 2:S2-4.

Ibaretta D, Bock AK, Klein C, Rodriguez-Cerezo E. Towards quality assurance and harmonisation of genetic services in the EU (IPTS-ESTO-European Commission Joint Research Centre document). EUR 20977, September 2003.

The UK Government White Paper ' Our Inheritance, Our Future - Realising the potential of genetics in the NHS', June 2003
(www.doh.gov.uk/genetics/whitepaper.htm)

Cotton RG. Methods in clinical molecular genetics. Eur J Pediatr. 2000;159 Suppl 3:S179-82.

Aymé S. Bridging the gap between molecular genetics and metabolic medicine: access to genetic information. Eur J Pediatr. 2000;159 Suppl 3:S183-5.

European Parliament. Draft report on the social, legal, eethical, and economical implications of human genetics. (Fiori. F., Rapporteur). EUR 447517
(<http://www.europarl.eu.int/meetdocs/committees/gene/20011105/447517en.pdf>)

France. LOI n° 2004-800 du 6 août 2004 relative à la bioéthique
(<http://www.legifrance.gouv.fr/WAspad/UnTexteDeJorf?numjo=SANX0100053L>)

Review of Ethical Issues in Medical Genetics. Report of Consultants to WHO. WHO Human Genetics Programme 2001.
(http://www.who.int/genomics/publications/en/ethical_issuesin_medgenetics%20report.pdf)

Weston AD, Hood L. Systems biology, proteomics, and the future of health care: toward predictive, preventative, and personalized medicine. J Proteome Res. 2004;3(2):179-96.

Joint Committee on Medical Genetics. Consent and Confidentiality in Medical Genetic Practice. October 2003
(<http://www.bshg.org.uk/Official%20Docs/JCMG%20Consent%20Confid%20draft%20report%201003.pdf>)

Websites:

The UK Biobank: <http://www.ukbiobank.ac.uk/>

UK Department of Health, information on genetics:

<http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Genetics/fs/en>

UK Government White Paper "'Our inheritance, our future - realising the potential of genetics in the NHS": www.doh.gov.uk/genetics/whitepaper.htm

The Breast Cancer Linkage Consortium: <http://www.humgen.nl/lab-devilee/bclchome.htm>

Annex 3: some reference books

AUTHOR / EDITOR	TITLE	PUBLISHER
Rainer Schulte	Patentgesetz mit Europäischem patentübereinkommen 6., neubearbeitete und erweiterte Auflage	Carl Heymans verlag
Eva-Maria Müller	Die Patentfähigkeit von Arzneimitteln – der gewerbliche Rechtsschutz für Pharmazeutische, mdizinische und bio technologische Erfindungen	Springer verlag
Heidi Von Weltzien Hoivik, Andreas Føllesdal	Ethics and Consultancy : European Perspectives	Kluwer Academic Publishers
Brian Bix	Jurisprudence : Theory and Context	Carolina Academic Press
Margarete Singer, Dieter Stauder	European Patent Convention volume 1 Substantive Patent Law, 3 rd edition	Sweet & Maxwell - Carl Heymans
O.C. McSwite	Legitimacy in Public Administration, a dicourse analysis	Sage Publications
Geertui Van Overwalle	Octrooirecht, ethiek en biotechnologie Patent Law, ethics and Biotechnology	Bruylant Brussel
Gavin Brooks	Biotechnology in Healthcare, an introduction to biopharmaceuticals	Pharmaceutical Press
S. Jeffery, J. Booth, S. Myint	Molecular Diagnosis	Bios Scientific Publishers
Peter S. Harper, Angus J. Clarke	Genetics Society and Clinical Practice	Bios Scientific Publishers
Rüdiger Wolfrum, Peter- Tobias Stoll, Stephanie Franck	Recht & Medizin : Die Gewährleistung freier Forschung an und mit Genen und das Interesse an der wirtschaftlichen Nutzung ihrer Ergebnisse vol 58	Peter Lang, Europäischer Verlag der Wissenschaften
David P. Mindell	Avian Molecular Evolution and Systematics	Academic Press
Diane L. Baker, Jane L. Schuette, Wendy R. Uhlman	A Guide to Genetic Counseling	Wiley-Liss, John Wiley & Sons, Inc.
Sven J.R. Bostyn	Enabling Biotechnological Inventions in Europe and the United States, A study of the patentability of proteins and DNA sequences with special emphasis on the disclosure requirement	European Patent Office

Legal Research Service	Case Law of the Boards of Appeal of the European Patent Office	European Patent Office
Allen Buchanan, Norman Daniels	From Chance to Choice, Genetics & Justice	Cambridge University Press
Dan W. Brock, Daniel Winkler		
Peter J. Bentley	Digital Biology	Simon and Schuster
Bernard Gert, Charles M. Culver	Bioethics, a return to fundamentals	Oxford University Press
K. Danner Clouser		
Stephen A. Merrill, Wesley M. Cohen	Patents in the knowledge-based economy	National Academic Press
Gerald Paterson	The European Patent System : The Law and Practice of the European Patent Convention, 2 nd ed.	Sweet & Maxwell
Gerals Kamstra, Nick Scott-Ram,	Patents on Biotechnological inventions : The E.C. directive	Sweet & Maxwell
Mark Döring, Andrew Sheard, Henry Wixon		
Carol Levine	Taking Sides, Clashing Views on Controversial Bioethical Issues, 8 th edition	Dushkin/McGraw-Hill
Cooper D.N. and Krawczak M.	Human Gene Mutation.	BIOS Scientific Publishers Ltd., 1993
Strachan T. and Read A.P.	Human Molecular Genetics	2 nd Ed. BIOS Scientific Publishers Ltd., 1999
Lewis R.	Human Genetics: Concepts and Applications	5 th Ed. McGraw Hill, 2003
Davies K. and White M.	Breakthrough. The race to find the breast cancer gene.	J. Wiley & Sons, Inc. 1995