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Datum/Date
17. 02. 09

Zeichen/Ref./Réf.	Anmeldung Nr./Application No./Demande n° //Patent Nr./Patent No./ Brevet n°.
K2709OPP(EP)S3	95305605.8 - 2405 / 0705903

Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire
The University of Utah Research Foundation

Appeal number: **T 0666/05 - 3304**

Please find enclosed a copy of the decision dated 13-11-2008.

PROC | DISP

The Registrar - P. Cremona
Tel.: 089 / 2399 - 3341

Annex(es):
Registered letter with advice of delivery

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Datum/Date
17. 02. 09

OPPO 02 - OPPO 03

Zeichen/Ref./Réf.		Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./ Brevet n°.
E18565-TER-FFP	OPPO 01	95305605.8 - 2405 / 0705903

Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire
The University of Utah Research Foundation

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Annex(es): 3 copies (O1 - O2 - O3)
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Datum/Date
17. 02. 09

Zeichen/Ref./Réf.		Anmeldung Nr./Application No./Demande n° //Patent Nr./Patent No./ Brevet n°.
K1873EP	OPPO 04	95305605.8 - 2405 / 0705903
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire		
The University of Utah Research Foundation		

Appeal number: **T 0666/05 - 3304**

Please find enclosed a copy of the decision dated 13-11-2008.

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The Registrar - P. Cremona
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Registered letter with advice of delivery

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Datum/Date
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Zeichen/Ref./Réf.		Anmeldung Nr./Application No./Demande n° //Patent Nr./Patent No./ Brevet n°.
BZ718BSW/CS	OPPO 05	95305605.8 - 2405 / 0705903

Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire
The University of Utah Research Foundation

Appeal number: **T 0666/05 - 3304**

Please find enclosed a copy of the decision dated 13-11-2008.

PROC | DISP

The Registrar - P. Cremona
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Datum/Date
17. 02. 09

Zeichen/Ref./Réf.	Anmeldung Nr./Application No./Demande n° //Patent Nr./Patent No./ Brevet n°.
OPPO 06	95305605.8 - 2405 / 0705903

Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire
The University of Utah Research Foundation

Appeal number: **T 0666/05 - 3304**

Please find enclosed a copy of the decision dated 13-11-2008.

PROC | DISP

The Registrar - P. Cremona
Tel.: 089 / 2399 - 3341

Annex(es):
Registered letter with advice of delivery

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0666/05 - 3.3.04

DECISION
of the Technical Board of Appeal 3.3.04
of 13 November 2008

Appellant I: (Patent Proprietor)
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Decision under appeal:

Interlocutory decision of the Opposition Division of the European Patent Office posted 09 June 2005 concerning maintenance of European patent No. 0705903 in amended form.

Composition of the Board:

Chair: U. Kinkeldey
Members: M. Wieser
D. S. Rogers
G. Alt
R. Moufang

Summary of Facts and Submissions

I. Appeals were lodged by the Patent Proprietor (Appellant I) and by Opponents 01 to 03 (Appellants II to IV) against the decision of the Opposition Division dated 9 June 2005 according to which European patent No. 0 705 903 could be maintained in amended form (Article 102(3) EPC 1973). The patent has the title "Mutations in the 17q-linked breast and ovarian cancer susceptibility gene" and claims priority from seven US applications, P1 to P7, of which the fourth P4 and the fifth P5 were filed on 29 November 1994 and 24 March 1995, respectively.

II. Six oppositions (Opponents 01 to 06) were filed against the patent covering the grounds of Article 100(a) in combination with Articles 52(2), 52(4), 53(a), 54, 56 and 57 EPC 1973, Article 100(b) in combination with Article 83 EPC 1973 and Article 100(c) in combination with Article 123(2) EPC 1973.

It is to be noted that the oppositions were filed before the entry into force of the EPC 2000 and therefore in the original notices of opposition all references to the Articles of the EPC were to the Articles of the EPC 1973. Taking into account the relevant transitional provisions, in this decision, instead of referring to Articles 52(2), 52(4), 53(a), 54, 56, 57, 83 and 123 EPC 1973, reference will be made to the corresponding Articles of the EPC 2000 that is Articles 52(2), 53(c), 53(a), 54, 56, 57, 83 and 123 EPC 2000 respectively, unless otherwise stated. Throughout this decision the EPC 2000 will be referred to as the EPC.

III. The Opposition Division decided that the subject-matter of claims 1 and 2 of the main request before it lacked novelty (Article 54 EPC) and, by exercising its discretion under Article 114(2) EPC, did not admit Patent Proprietor's auxiliary request I into the procedure, which was filed at the oral proceedings before it. Further it decided that the claims of auxiliary request II did not comply with Articles 123(2) and 84 EPC. However, the Opposition Division decided that claims 1 to 3 of Patent Proprietor's auxiliary request III, filed during the oral proceedings, met all requirements of the EPC.

IV. The Board dispatched a communication dated 21 January 2008, wherein the parties where asked whether they maintained their actual requests in the light of decision T 1213/05 of 27 September 2007, posted on 12 December 2007.

V. Oral proceedings before the Board took place on 12 and 13 November 2008.

Appellant I requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 9 of the main request filed with a letter dated 2 June 2008.

The Appellants II to IV (Opponents 01 to 03) requested that the decision under appeal be set aside and that the patent be revoked.

Opponents 04 to 06, which are parties as of right according to Article 107 EPC, also requested that the

decision under appeal be set aside and that the patent be revoked.

VI. Claim 1, 2 and 7 of the main request read as follows:

"1. A method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is germline alteration 185delAG -> ter39 in the BRCA1 gene in a tissue sample of said subject, said alteration indicating a predisposition to said cancer.

2. A method for diagnosing a breast or ovarian lesion of a human subject for neoplasia associated with the BRCA1 gene locus which comprises determining whether there is mutation 185delAG -> ter39 in the BRCA1 gene in a sample from said lesion.

7. A nucleic acid probe having 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG -> ter39."

Claims 3 to 6 refer to preferred embodiments of the methods according to claims 1 and 2. Claim 8 refers to a replicative cloning vector comprising the nucleic acid of claim 7 and claim 9 to a host cell transformed with the vector of claim 8.

VII. The following documents are mentioned in the present decision:

D1: Miki et al., Science (Oct. 1994) 266: 66-71

D5: Shattuck-Eidens et al., JAMA (Feb. 1995) 273: 535-541

D6: Simard et al., Nature Genetics (Dec. 1994) 8: 392-398

D9: Kelsell et al., Hum. Mol. Genet. (1993) 2: 1823-1828

D17: Information concerning GenBank Sequence, Accession number U14680

D29: Tonin et al., Am. J. Hum. Genet. (1995) 57: 189

D42: Feunteun et al., Am. J. Hum. Genet. (1993) 52: 736-742

D47: Extracts from the BIC database

D96: Editorial, Nature Genetics (Dec. 1994) 8: 310

D100: Declaration of Dr Critchfield of 22 November 2004

D115: Menczer et Ben-Baruch, Obstet. Gynecol. (1991) 77: 276-277

D116: Modan et al., JAMA (Dec. 1996) 276: 1823-1825

D117: Wooster et al., Science (Sep. 1994) 265: 2088-2090

D119: Overview of the frequency of BRCA1 mutations in European countries

D144: Declaration of Dr Critchfield of 9 October 2008

VIII. The submissions made by Appellant I can be summarized as follows:

Amendments (Article 123(2) and (3) EPC)

The amendments in claims 1 and 2 were supported by the application as filed, e.g. by the originally filed claims 17 and 18 in combination with Table 14 on page 57 of the description. To single out a single mutation from a list of thirty-four mutations resulted in a restriction of the scope of protection (Article 123(3) EPC) and could not be considered as an amendment violating the requirements of Article 123(2) EPC. The omission of a reference to SEQ ID NO: 1 and wild type allelic variants thereof did not introduce new matter. It was an established principle that a compound known in the art (the BRCA1 gene) needed not to be structurally defined in a claim if it could be referred to by using a generally accepted designation.

Clarity (Article 84 EPC)

The relevant date was the filing date of the fourth priority document P4. At that date the structural formula, i.e. the coding sequence of the BRCA1 gene, was known from the disclosure in document D1 in connection with document D17. Based on this disclosure in the prior art and in the patent in suit, the skilled

person was enabled to determine whether the mutation 185delAG -> ter39 was present in the BRCA1 gene. Thus the claims were clear and met the requirements of Article 84 EPC.

Priority right (Article 87 EPC 1973 and Articles 88 and 89 EPC)

The methods according to claims 1 and 2 relied on the detection of the mutation 185delAG -> ter39. The same invention was disclosed in priority document P4 (see claims 1 and 3 and Table 14 on page 92 of P4). Although the nucleic acid probe of claim 7, due to the term "having", might contain a nucleotide sequence in addition to the 15 to 30 nucleotides of SEQ ID NO:1 containing the 185delAG -> ter39 mutation, this additional sequence was not necessarily one derived from SEQ ID NO:1. Also priority document P4 used the term "having" in order to define probes (see page 29, lines 5 to 7 of P4). Therefore claims 1 to 9 were entitled to claim priority from priority document P4.

Novelty (Article 54 EPC)

As the claims were entitled to claim priority from priority document P4, there was no relevant prior art on file for the assessment of novelty. The requirements of Articles 54 EPC were thus met.

Inventive step (Article 56 EPC)

The closest state of the art was represented by document D1. The problem underlying the patent in suit was the identification of a mutation that allowed the

provision of an effective screening method. The identification of the 185delAG -> ter39 mutation, which was an extremely frequent mutation, to which none of the available prior art documents contained any information or hint, was considered to be a "lucky strike". At the best document D1 contained an invitation to start a scientific research program to find such mutation. As it was not predictable at all that such mutation existed, its detection was based on an inventive step as required by Article 56 EPC.

The objections raised under Articles 52(2) EPC, 52(4) EPC 1973, 53(a) and 57 EPC lacked substantiation and should be rejected by the Board.

IX. The submissions made by Appellants II to IV and Opponents 04 to 06 can be summarized as follows:

Amendments (Article 123(2) and (3) EPC)

To single out one specific mutation from a list of thirty four mutations was an amendment contravening the requirements of Article 123(2) EPC.

Claim 16 as granted contained a step of comparison with the reference molecule SEQ ID NO: 1 or a wild-type allelic variant thereof. The omission of this reference step violated the requirements of Article 123(3) EPC. This was because claim 1 now encompassed also the comparison with non-wild-type allelic variants of the gene. Contrary to Appellant I's argument, the BRCA1 gene was an unknown compound at the relevant priority date (P4) and thus needed to be structurally defined when mentioned in a patent claim.

Clarity (Article 84 EPC)

The diagnostic method of claim 1 did not refer to an identifiable reference sequence and thus missed an essential feature.

A further missing feature was the identification in the claim of the specific population group in which the germline alteration 185delAG -> ter39 appeared with high frequency, namely the Ashkenazi Jewish people.

The use of the term "BRCA1 gene" in claim 1 had the result that it was no longer clear what fell within the scope of the claim, as this term itself was not clear at the filing date of priority document P4.

Finally, claims 1 and 2 were not supported by the description.

Priority right (Article 87 EPC 1973 and Articles 88 and 89 EPC)

From priority document P4 it was not possible either to identify the definite BRCA1 cDNA sequence or the localization of the 185delAG -> ter39 mutation.

The claims could only enjoy priority right from priority document P5, being the earliest of the seven priority documents disclosing SEQ ID NOs: 1 and 2 corresponding exactly to SEQ ID NOs: 1 and 2 as disclosed in the application as filed.
Deciding differently would not only contradict decision T 1213/05 (supra) but also the gist of decision G 2/98 of the Enlarged Board of Appeal (OJ EPO 2001, 413).

Such possible contradiction could not be justified by the argument that present claim 1 did not refer to a substance, but to a diagnostic method using it. Anyhow, such argument would not apply to claim 7 referring to a nucleic acid probe and explicitly referring to SEQ ID NO: 1.

Novelty (Article 54 EPC)

As a consequence, documents D5 and D6, both published between priority documents P4 and P5, belonged to the state of the art and thus anticipated the claimed subject-matter.

Inventive step (Article 56 EPC)

Even if the claims were entitled to claim priority from priority document P4, there was no inventive step. The closest prior art was represented by document D1, disclosing the BRCA1 sequence and already showing several mutations thereof. The problem to be solved was therefore the provision of an alternative mutation of the BRCA1 gene. Upon combination of the teaching in document D1 with the disclosure in document D115 the finding of the 185delAG -> ter39 mutation was inevitable and any unexpected advantage represented simply a bonus effect which could not substantiate a finding of an inventive step according to EPO case law.

The inventors had carried out the necessary experimentation faster than others merely because they had been able to put more money and manpower into the project, but this did not justify the recognition of an inventive step. Suitable kindreds were also available

to other scientific groups, and sooner or later one of these groups would have been successful as well. Any problems that might have been encountered in the course of the project would have been overcome by the skilled person using conventional means.

The problem to be solved had been reformulated during the opposition procedure, namely to be the provision of a diagnostic method for detecting a particularly frequent mutation in the BRCA1 gene. This problem was not derivable from the application as originally filed. Accordingly the reformulation was not acceptable in the light of the established case law of the Boards of Appeal.

Moreover, the reformulated problem had not been solved over the entire scope of the claims, as the germline alteration 185delAG -> ter39 appeared with high frequency in a very limited part of the human population only. In the rest of the human population this mutation when used in a diagnostic method did not give rise to any "surprising effect" due to its low frequency.

Patentable inventions, exceptions to patentability, industrial applicability

Although the claimed diagnostic methods were practised on tissue samples, the logical link between the sample and the human body has not been broken. Claims 1 to 6 therefore did not refer to patentable inventions according to Article 53(c) EPC.

The commercial exploitation of the patent was unethical. The subject-matter of claims 1 to 6 contravened the requirements of Article 53(a) EPC.

Claim 7 referred to a fragment of the human genome which was not a patentable invention according to Article 52(2) EPC. The nucleic acid probe according to claim 7 had no industrial applicability, contrary to the requirements of Article 57 EPC.

Reasons for the Decision

For ease of reading if reference is made, either individually or collectively, to Appellants II to IV (Opponents 01 to 03) and the other parties (Opponents 04 to 06), such reference shall be to "the Opponents".

1. The appeals are admissible.

Main Request

Clarity (Article 84 EPC)

2. The claims of the main request differ from the claims as granted and it must thus be assessed whether they fulfil the requirements of Article 84 EPC in so far as the amendments are concerned.

3. The Opponents have argued that claims 1 and 2 were unclear, because they did not refer to the nucleotide sequence set forth in SEQ ID NO: 1 as the reference sequence, in contrast to the claims originally filed and granted. The term "BRCA1 gene" used in claims 1 and

2 was unclear, as the prior art disclosures of the exact sequence of this gene had changed over time.

4. As concerns the term "BRCA1 gene", the description of the patent in suit states that this term refers to "polynucleotides, all of which are in the BRCA1 region, that are likely to be expressed in normal tissue, certain alleles of which predispose an individual to develop breast, ovarian, colorectal and prostate cancer" (page 14, lines 45 to 47), and that "[t]he coding sequence for a BRCA1 polypeptide is shown in SEQ ID NO:1" (page 14, lines 55 to 56).

Furthermore, documents D1 and D17, which were available to the public at the fourth priority date of the patent in suit, refer to the BRCA1 gene. The fourth priority document of the patent in suit is the earliest priority document in which the mutation 185delAG -> ter39 is mentioned (see Table 14 on page 92). The subject-matter of claims 1 and 2 of the main request relating to the determination of this mutation, can thus not be entitled to a priority date earlier than the fourth priority date, and this has not been contested by Appellant I. Document D1 describes the identification of the BRCA1 gene and discloses in Figure 2 the predicted amino acid sequence for BRCA1. In the legend to Figure 2, it is stated that the BRCA1 nucleotide sequence was deposited in GenBank with accession number U14680; this GenBank entry is part of document D17. The patent in suit also refers to said GenBank entry and states on page 43, lines 50 to 51 that the "sequence of the BRCA1 cDNA (up through the stop codon) has also been deposited with GenBank and assigned accession number U-14680".

In view of these disclosures in the patent in suit and in the prior art, the Board is convinced that the term "BRCA1 gene" would already have been clear to a skilled person at the earliest possible priority date. The skilled person would also know from his/her common general knowledge that the alteration termed "185delAG -> ter39" referred to a deletion of the nucleotides "AG" in position 185, which would result in a stop-codon in codon number 39. In the nucleotide sequence of the BRCA1 gene shown in SEQ ID NO: 1 of the patent in suit and in the GenBank entry U-14680 of document D17, the nucleotides "AG" do indeed occur in position 185.

5. With respect to the Opponents' argument that the prior art disclosures of the sequence of the BRCA1 gene had changed over time, the Board notes that no evidence has been presented by the Opponents that there have been any changes in the disclosures of the BRCA1 gene sequences in positions 185 and 186, which are the relevant positions when carrying out the methods of claims 1 and 2. Given the disclosures of the BRCA1 gene sequences in SEQ ID NO: 1 of the patent in suit and in document D17 of the prior art, the Board is convinced that it would be clear to the skilled person that the presence of the mutation 185delAG -> ter39 in the BRCA1 gene could be determined by establishing whether the nucleotides "AG" of the positions corresponding to numbers 185 and 186 are present or absent in the nucleotide sequence of the sample, and that there is thus no lack of clarity in claims 1 and 2.

6. The Opponents have further argued that claims 1 and 2 were not supported by the description and did not state the essential features of the invention, because these

claims did not state what the reference BRCA1 sequence was.

7. The Board cannot follow this argument but is convinced that the skilled person would know the BRCA1 gene sequence, both from the patent in suit and from the prior art, and would be able to use this knowledge to determine whether the mutation 185delAG -> ter39 is present or absent in a sample. Further information on how the claimed diagnostic methods can be carried out is disclosed for instance in the passage from page 20, line 7 to page 21, line 15 of the description of the patent in suit.

8. It has furthermore been argued by the Opponents that claims 1 and 2 did not state all the essential features of the claimed invention, contrary to Article 84 EPC. The mutation 185delAG -> ter39 was not the most important mutation in most European countries, as evidenced by document D119, but occurred at a high frequency only in people of Ashkenazi Jewish descent, as shown by document D29. Screening for this mutation would only make sense in a population where it was frequently occurring. According to the established case law of the Boards of Appeal, all features which are necessary for solving the technical problem with which the patent is concerned were to be regarded as essential features, which had to be indicated in the claims; therefore the target group had to be included into the relevant claims.

9. The Board cannot agree with the Opponents that claims 1 and 2 do not state all the essential features of the invention. In the Board's view the invention is not

directed to methods for screening a human population. Instead, the invention relates to methods for diagnosing either a predisposition for breast and ovarian cancer (claim 1) or a breast and ovarian lesion for neoplasia (claim 2) **in/of a human subject.** Therefore the Board is convinced that the determination of the presence of the mutation 185delAG -> ter39 in the BRCA1 gene in a sample of a human subject would allow the claimed diagnosis. Thus, the Board cannot recognize any lack of essential features in claims 1 and 2.

10. The Opponents also submitted that claim 7 lacked clarity, because due to the use of the term "having", which had to be interpreted as "comprising", the claim was indefinite and thus unclear.

11. The Board agrees that the term "having" in claim 7 has to be interpreted as meaning "comprising", but cannot recognize that this results in a lack of clarity of the claim. The skilled person reading the claim would understand that the claimed nucleic acid probe comprises 15 to 30 nucleotides of SEQ ID NO: 1 and contains the mutation 185delAG -> ter39, and can also comprise other, additional sequences.

12. Therefore, the requirements of Article 84 EPC are met.

Added matter (Article 123(2) EPC)

13. Article 123(2) EPC requires that a European patent application or a European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed.

In accordance with the established case law of the Boards of Appeal, the content of an application is the disclosure that is directly and unambiguously derivable from this application.

14. Claim 1 of the main request relates to a "method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is germ line alteration 185delAG -> ter39 in the BRCA1 gene in a tissue sample of said subject, said alteration being indicative of a predisposition to said cancer".

15. Claim 17 of the application as filed relates to a "method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is a germ line alteration in the sequence of the BRCA 1 gene in a tissue sample of said subject compared to the nucleotide sequence set forth in SEQ. ID No: 1 or a wild-tyle [*sic*] allelic variant thereof, said alteration indicating a predisposition to said cancer being selected from the mutations as set forth in Tables 12, 12A and 14".

In Table 14 of the application as filed, the mutation 185delAG -> ter39 is one of the mutations listed.

Claim 1 of the main request thus differs from claim 17 of the application as filed in that only one of the mutations set forth in Tables 12, 12A and 14, i.e. the mutation 185delAG -> ter39, is mentioned, and in that it lacks the phrase "compared to the nucleotide

sequence set forth in SEQ. ID No: 1 or a wild-tyle [*sic*] allelic variant thereof".

16. The Opponents have argued that the selection of only one specific mutation out of the long list of mutations set forth in Tables 12, 12A and 14 was not directly and unambiguously derivable from the application as filed, which only disclosed methods for testing for a plurality of mutations, for instance in the passages on page 2, lines 3 to 7; page 5, lines 2 to 8 and 45 to 52, and page 19, lines 3 to 9 of the application as filed (published version), which referred to the plural form of "alleles" and "mutations". Therefore, claim 1 did not comply with Article 123(2) EPC.

17. The Board cannot follow this argument, because claim 17 of the application as filed states that the claimed method comprises determining whether there is **a germ line alteration** in the sequence of the BRCA1 gene, **said alteration** being selected from the mutations set forth in Tables 12, 12A and 14. Determining in the claimed method only one of any of the specific mutations listed in Tables 12, 12A and 14, for instance the second mutation of Table 14, 185delAG -> ter39, is thus disclosed in the application as filed.

18. The Opponents have furthermore argued that claim 1 contravened Article 123(2) EPC because the application as filed only disclosed methods comprising a step of comparison with the nucleotide sequence set forth in SEQ ID No: 1 or a wild-type allelic variant thereof, which step was not stated in claim 1 of the main request.

19. The Board considers that the expression "compared to the nucleotide sequence set forth in SEQ ID No: 1 or a wild-type allelic variant thereof" in claim 17 as filed does not define an actual step of comparison to be carried out in the claimed methods, but only serves as a reference in the definition of the alteration that is to be determined (see also point (28) infra). When determining whether there is mutation 185delAG -> ter39 in a tissue sample, the skilled person would always establish whether or not the nucleotides "AG" in positions 185 and 186 of the BRCA1 gene are absent in the sequence of the patient's sample, and there would be no difference if the method was carried out in accordance with the method of claim 17 as filed or in accordance with the method of claim 1 of the main request. Therefore, the subject-matter of claim 1 is directly and unambiguously derivable from the application as filed.

20. Accordingly, the subject-matter of claim 2 can be derived from claim 18 of the application as filed. As concerns the dependent claims 3 to 6, the subject-matter of claim 3 can be derived from claims 19 to 21 and 23 as filed, claim 4 can be derived from claims 22 and 23 as filed, claim 5 can be derived from claim 26 as filed, and claim 6 can be derived from claim 25 as filed.

21. With respect to claim 7, the Opponents have argued that the length of the claimed "nucleic acid probe having 15 to 30 nucleotides of SEQ ID NO: 1 and containing the mutation 185delAG -> ter39" was not disclosed in the application as filed, and that, therefore, the claim did not comply with Article 123(2) EPC.

22. Claim 4 of the application as filed relates to a "nucleic acid probe wherein the nucleotide sequence is a portion of a nucleic acid as claimed in any one of claims 1 to 3 including a mutation or polymorphism compared to the nucleotide sequence set forth in SEQ.ID No: 1 selected from the mutations set forth in Tables 12, 12A and 14 and the polymorphisms set forth in Tables 18 and 19", but does not specify a length of 15 to 30 nucleotides. With respect to the disclosure of this length, the Board can follow Appellant I's argument that because the application as filed discloses on page 14, lines 19 to 22 the broad range of "at least about five codons (15 nucleotides)", and page 11, lines 13 to 15 discloses the single value of "30 nucleotides", the range of "15 to 30 nucleotides" was directly and unambiguously derivable from the application as filed, in accordance with the established case law of the Boards of Appeal (see for instance decisions T 201/83, OJ EPO 1984, 481, point (7) and T 925/98 of 13 March 2001, point (2)). Thus, claim 7 fulfils the requirements of Article 123(2) EPC.

23. The subject-matter of claims 8 and 9 is disclosed in claims 5 and 7 of the application as filed, respectively.

24. Consequently, claims 1 to 9 comply with Article 123(2) EPC.

Extension of scope (Article 123(3) EPC)

25. According to Article 123(3) EPC, a patent may not be amended in such a way as to extend the protection it confers.

26. Claims 16 and 17 as granted relate to diagnostic methods which comprise determining whether there is a alteration in the sequence of the BRCA 1 gene in a tissue sample compared to the nucleotide sequence set forth in SEQ ID NO: 1 or a wild-type allelic variant thereof, said alteration being selected from a list of 34 specific mutations, one of which is the mutation 185delAG -> ter39.

Claims 1 and 2 of the main request relate to diagnostic methods which comprise determining whether there is the mutation 185delAG -> ter39 in the BRCA 1 gene in a tissue sample. In contrast to claims 16 and 17 as granted, claims 1 and 2 of the main request do not contain the expression "compared to the nucleotide sequence set forth in SEQ ID NO: 1 or a wild-type allelic variant thereof".

27. The Opponents have argued that, due to the absence of said expression in the claims of the main request, there was an extension of scope of protection, contrary to Article 123(3) EPC, firstly because the methods now claimed lacked a comparison step with the full-length sequence, which step was mandatory in the methods of claims 16 and 17 as granted, and secondly because the reference for determining the mutation in the methods of the main request now also included non-wild-type allelic variants of the nucleotide sequence set forth

in SEQ ID NO: 1, and was thus broader than in the claims as granted.

28. The Board does not share the Opponents' interpretation of the claims as granted and considers that the expression "compared to the nucleotide sequence set forth in SEQ ID NO: 1 or a wild-type allelic variant thereof" in claims 16 and 17 as granted does not mean that the claimed methods actually comprise a step of "comparing" the entire sequence of the BRCA1 gene with the sequence of SEQ ID NO: 1 or a wild-type allelic variant thereof (see point (19) above). Instead, SEQ ID NO: 1 is used in said claims only as a reference for defining the specific mutations listed, inter alia the mutation 185delAG -> ter39. The determination of this mutation is the same in the methods of the claims as granted and in the methods of the claims of the main request which do not refer to SEQ ID NO: 1; in both cases, a skilled person would establish whether or not the nucleotides "AG" in positions 185 and 186 of the BRCA1 gene are absent in the sequence of the patient's sample.

29. The Board's interpretation that claims 16 and 17 as granted do not comprise a mandatory step of comparing the entire sequence of the BRCA1 gene present in the patient's sample with the sequence of SEQ ID NO: 1 or a wild-type allelic variant thereof is further supported by dependent claims 20 to 22 and 24 as granted.

Claims 20 and 21 as granted, which are directly or indirectly dependent on claims 16 and 17, state that an oligonucleotide BRCA1 gene probe is contacted with mRNA or genomic DNA from the sample, and hybridization of

said probe is determined. Claim 22, which is dependent on claims 20 and 21, defines the probe as "an allele-specific probe for a mutant BRCA1 allele". The skilled person would understand that a method in which an allele-specific probe is used to determine a specific mutation would not comprise the comparison of the full-length gene sequence of the patient with SEQ ID NO: 1 or a wild-type allelic variant thereof as a mandatory feature.

Furthermore, claim 24 as granted, which is dependent on claims 16 and 17, states that "all or part of the BRCA1 gene in said sample is amplified and the sequence of said amplified sequence is determined". The Board considers that the amplification of only part of the BRCA1 gene would not make sense to a skilled person if the method required that the entire gene sequence would have to be compared with the sequence of SEQ ID NO: 1 or a wild-type allelic variant thereof. Although it may theoretically be possible to interpret the expression "part of the BRCA1 gene" in claim 24 as granted as referring only to the case where all exon sequences are amplified, which would then allow the comparison with the entire sequence of SEQ ID NO: 1 or a wild-type allelic variant thereof, the Board is convinced that this would not be the skilled person's understanding of claim 24 read in combination with independent claims 16 and 17.

30. The Board thus concludes that the methods of claims 16 and 17 as granted do not comprise a mandatory comparison step with the entire nucleotide sequence of SEQ ID NO: 1 or a wild-type allelic variant thereof, and that the lack of such a step in the methods of

claims 1 and 2 of the main request cannot result in an extension of scope of protection.

31. The Board can also not recognize any extension of the scope of protection due to a broadening of the definition of the reference sequence used. It follows from the definition given on page 14, lines 45 to 51 of the patent in suit, that the term "BRCA1 gene" referred to in claims 1 and 2 of the main request encompasses all allelic variations of the DNA sequence, including mutated, non-wild type forms, which are not encompassed by the expression "nucleotide sequence set forth in SEQ ID No: 1 or a wild-type allelic variant thereof" referred to in claims 16 and 17 as granted. However, this difference does not affect the scope of the claims, since in order to determine whether the mutation 185delAG -> ter39 is present in the sequence of a patient's sample, the skilled person would only establish whether the nucleotides "AG" in positions 185 and 186 of the BRCA1 gene are absent or not. For this determination, it does not matter whether SEQ ID NO: 1 or wild-type allelic variants thereof are used as the reference nucleotide sequence or whether the reference sequence would contain additional mutations.

32. The Board cannot follow the Opponents' argument that claims 1 and 2 of the main request now covered the case where a comparison of the sequence of the patient's sample was made with a 185delAG -> ter39 mutant sequence and would thus entail a different, i.e. false result, in contrast to the methods of claims 16 and 17 as granted. The Board is convinced that a skilled person aiming at diagnosing a patient by determining whether there is the mutation 185delAG -> ter39 in the

BRCA1 gene in a tissue sample would not make this determination on the basis of a reference sequence already having the mutation that is to be determined. This would go against his/her common general knowledge and would not make any sense. According to established case law of the Boards of Appeal, a skilled person should try to arrive at an interpretation of a claim which is technically sensible and takes into account the whole disclosure of the patent (see decisions T 190/99 of 6 March 2001, point (2.4) and T 1241/03 of 1 September 2005, point (9)).

33. In view of the above, the requirements of Article 123(3) EPC are fulfilled.

Priority right (Article 87 EPC 1973 and Articles 88 and 89 EPC)

34. Documents D5 and D6 are scientific publications dated February 1995 and December 1994, respectively, thus published between the filing dates of the fourth priority document P4 (US 348824; 29 November 1994) and the fifth priority document P5 (US 409305; 24 March 1995). It is undisputed that the disclosure in these documents, if it belonged to the state of the art under Article 54(2) EPC, would be highly relevant for the issues of novelty (Article 54 EPC) and/or inventive step (Article 56 EPC) of the claimed subject-matter.

Documents D5 and D6 would not belong to the state of the art under Article 54(2) EPC if the claims were entitled to claim priority from the fourth priority document P4.

35. The right to priority is governed by Article 87 EPC 1973, which requires that the European patent (application) and the application whose priority is claimed relate to the same invention. Article 88(3) EPC further specifies that, if one or more priorities are claimed in respect of a European patent application, the right of priority shall cover only those elements of the application which are included in the respective priority application(s).

36. According to the Opinion G 2/98 of the Enlarged Board of Appeal (OJ EPO 2001, 413, point (9)), the requirement for claiming priority of "the same invention", referred to in Article 87(1) EPC 1973, means that the priority of a previous application in respect of a claim in a European patent application in accordance with Article 88 EPC is to be acknowledged only if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole.

37. The fourth priority document P4 discloses a method for diagnosing a predisposition to breast and ovarian cancer in a human comprising the detection of an alteration in the BRCA1 gene, said alteration indicating a predisposition to said cancer and being selected from the group consisting of the mutations set forth in Table 14 (see page 5, lines 26 to 29 and claims 1 and 3), whereby the first mutation of the list in Table 14 is the mutation 185delAG -> ter39.

However, the nucleotide sequence of the cDNA coding for BRCA1 as disclosed in SEQ ID NO: 1 of the fourth

priority document P4 deviates from the corresponding sequence disclosed in SEQ ID NO: 1 of the patent in suit by 15 nucleotide residues. These deviations in the BRCA1 coding sequence are listed in Exhibit 1 (Table 1) of document D144 submitted by Appellant I with his letter dated 10 October 2008. Nine of these deviations lead to an amino acid change in the amino acid sequence of SEQ ID NO: 2, while six are "silent deviations" which do not result in amino acid changes. Thus, the 1863 amino acid long sequence of the BRCA1 protein shown in SEQ ID NO: 2 of the fourth priority document P4 deviates from the corresponding sequence disclosed in SEQ ID NO: 2 of the patent in suit in 9 amino acid positions. None of the 15 nucleotide changes is an insertion or a deletion or results in a stop codon. Within the BRCA1 coding sequence, the first of the 15 deviations occurs in nucleotide position 1364, corresponding to codon number 415.

The earliest priority document disclosing the nucleotide sequence coding for BRCA1 and the amino acid sequence of the encoded protein, which are identical to SEQ ID NOs: 1 and 2 disclosed in the patent in suit and in the application as filed, is the fifth priority document P5.

38. The Opponents have argued that because of the above mentioned differences in the nucleotide and amino acid sequences between the fourth priority document P4 and the patent in suit, only the fifth priority could be accorded to the claims of the main request.

39. With respect to claim 1, the Opponents have argued that in view of said sequence differences, the meaning of

the term "BRCA1 gene" differed between the fourth priority document, P4, and the patent in suit, and because the BRCA1 gene was a technical feature of the claim, the claimed invention could not be directly and unambiguously derived from the fourth priority document P4.

40. The Board cannot follow this line of argument. The invention claimed in claim 1 is a diagnostic method which comprises determining whether there is germline alteration 185delAG -> ter39 in the BRCA1 gene. In order to determine in the claimed method whether there is the mutation 185delAG -> ter39, it is not required to determine any kind of difference between the patient's nucleotide or amino acid sequence and a reference sequence. It is only required to determine whether there is a deletion of the nucleotides "AG" in positions 185 and 186 of the BRCA1 gene. Neither this mutation 185delAG -> ter39, nor the nucleotides of the BRCA1 gene in the relevant positions 185 and 186 have changed between the fourth priority document P4, the fifth priority document P5 and the patent in suit. In fact, the first nucleotide in the BRCA1 sequence which deviates between the fourth priority document P4 on the one hand and the fifth priority document P5 and the patent in suit on the other hand is in position 1364, thus more than 1000 nucleotides downstream of the positions that are looked at in the claimed method. The above mentioned sequence differences thus do not have any impact on the actual invention claimed. The mutation to be detected with the method of claim 1 is exactly the same, irrespective of whether the sequence information disclosed in the fourth priority document

P4, the fifth priority document P5 or the patent in suit is used as a reference.

41. The Opponents have also argued that SEQ ID NO: 1 of the fourth priority document P4 did not have the nucleotides "AG" in position 185, and that there was a severe ambiguity within this priority document because the footnote 2 of Table 14 referred to the BRCA1 sequence in GenBank under accession number U14680. The Opponents submitted that from its first release onwards, this GenBank entry had disclosed the "correct" BRCA1 sequence disclosed in the fifth priority document and the patent in suit which thus differed from the sequence of SEQ ID NO: 1 of the fourth priority document. There was thus no clear and unambiguous disclosure of the invention now claimed in the fourth priority date.

42. The Board notes that SEQ ID NO: 1 of the fourth priority document P4 lacks the 56 nucleotides that are present at the 5' end of SEQ ID NO: 1 of the patent in suit, resulting in a different numbering of the nucleotides. In SEQ ID NO: 1 of the fourth priority document P4, the nucleotides "AG" that are deleted in the mutation 185delAG -> ter39 occur in position 129 instead of position 185. By contrast, Table 14 of the fourth priority document P4 refers to the mutation 185delAG -> ter39, and states in footnote 2 that "[n]ucleotides refer to the BRCA1 cDNA sequence in GENBANK under Accession No. U-14680". It has not been contested by any of the parties that in this sequence as released before the fourth priority date, nucleotide position 185 corresponds to the "AG" that is deleted in

the mutation 185delAG -> ter39 as disclosed in the patent.

The Board considers that a skilled person reading the fourth priority document would have easily recognized by a simple sequence comparison that the nucleotides in SEQ ID NO: 1 of this priority document and in the sequence of GenBank entry U14680 are differently numbered, and that position 185 of the mutation in Table 14 would correspond to position 129 of SEQ ID NO: 1. In this way, the skilled person would have been able to identify the exact location of the 185delAG -> ter39 mutation also in the sequence of SEQ ID NO: 1. The Board is therefore convinced that the skilled person would not have had problems to perform the method of claim 1 on the basis of the information given in the fourth priority document P4.

43. It was a matter of dispute between the parties whether the GenBank entry U14680 when it first became available to the public on 8 October 1994 disclosed a BRCA1 nucleotide sequence which contained the same sequencing "errors" as the nucleotide sequence of SEQ ID NO: 1 of the fourth priority document P4, or the "correct" nucleotide sequence as shown in SEQ ID NO: 1 of the fifth priority document and the patent in suit. Since, however, the sequence deviations under discussion do in any case not occur in the region of the mutation 185delAG -> ter39, and thus do not affect the claimed invention, the issue of the exact disclosure of the GenBank entry U14680 of 8 October 1994 is not relevant for the present case and need not be decided by the Board.

44. The Board is thus convinced that the invention of claim 1 is directly and unambiguously derivable from the fourth priority document P4 and enjoys the fourth priority date.

45. In view of page 5, lines 27 to 29 and page 37, lines 4 to 6 of the fourth priority document P4, the reasons given above as to why the subject-matter of claim 1 enjoys the fourth priority date apply analogously also for the subject-matter of claim 2. Furthermore, the subject-matter of claims 3 to 6 is disclosed in claims 5, 7, 8 and 10 and on page 18, lines 10 to 20 of the fourth priority document P4.

46. With respect to claim 7, the Opponents have argued that its subject-matter was not entitled to the fourth priority date because due to the use of the term "having", which had to be interpreted as meaning "comprising", the claimed nucleic acid probe could also comprise those nucleotides of SEQ ID NO: 1 which differed between the fourth priority document P4 and the patent in suit. SEQ ID NO: 1 was thus a technical feature of the claim, which feature was not disclosed in the fourth priority document P4.

47. It has not been contested by Appellant I that the term "having" in claim 7 is to be interpreted as meaning "comprising", and the Board concurs with this interpretation. Therefore, claim 7 does indeed encompass nucleic acid probes which, in addition to the "15 to 30 nucleotides of SEQ ID NO: 1", comprise any other nucleotide sequences. These sequences include parts of SEQ ID NO: 1 which lie outside the region of the mutation 185delAG -> ter39 and which differ

between the fourth priority document P4 and the patent in suit, or any other additional sequences unrelated to the BRCA1 gene.

48. The Board considers that these additional, non-defined sequences, whose presence in the claimed nucleic acid probe is entirely optional, do not define the actual invention that is claimed. The claimed invention is defined as a nucleic acid probe which has 15 to 30 nucleotides of SEQ ID NO: 1 and contains the mutation 185delAG -> ter39. With respect to these features defining the claimed invention, the disclosures of the fourth priority document P4, the fifth priority document P5 and the patent in suit are identical, the first nucleotide deviation in the sequence of SEQ ID NO: 1 occurring in position 1364. Therefore, the Board is convinced that the invention of claim 7 enjoys the fourth priority date.

49. As concerns claims 8 and 9, their subject-matter is disclosed on page 26, lines 8 to 11 of the fourth priority document.

50. The Board thus concludes that the subject-matter of claims 1 to 9 of the main request enjoys the fourth priority date and that, consequently, documents D5 and D6 do not constitute prior art under Article 54(2) EPC.

51. It was repeatedly argued by the Opponents that to decide along the lines argued above would be incompatible with decision T 1213/05 (supra). However, with respect to the question of priority rights, the situation in the present case differs from the one dealt with in decision T 1213/05 (supra) in the context

of auxiliary request II then before that Board, which concerned product claims and where the amino acid sequence of SEQ ID NO: 2 was a technical feature of the claimed invention (see points 19 to 34 of said decision).

In the present case, the claimed invention relates to the determination of a specific mutation, 185delAG -> ter39, and to certain probes containing said mutation, and this invention does not differ between the fourth priority document P4, the fifth priority document P5 and the patent in suit, for the reasons given above.

Novelty (Article 54 EPC)

52. As a consequence of the above decision on right to priority, documents D5 and D6, which are the only documents the Opponents relied on in the written procedure when objecting to the novelty of the claimed subject-matter, do not belong to the state of the art under Article 54(2) EPC.

53. The Opponents have thus not objected to the novelty of the claimed subject-matter on the basis of any document which belongs to the state of the art under Article 54(2) EPC.

As the Board also has no objections in this respect, the subject-matter of claims 1 to 9 is considered to be novel and to meet the requirements of Article 54 EPC.

Inventive step (Article 56 EPC)

54. The closest prior art is represented by document D1 which discloses the identification of the BRCA1 gene by positional cloning. Table 2 of the document discloses four predisposing mutations in BRCA1. The mutation 185delAG -> ter39 is not mentioned in document D1.

55. Having regard to document D1, the technical problem to be solved is the provision of a mutation that allows the development of an effective screening for inherited breast and ovarian cancer.

56. The Board is satisfied that this problem has been solved by the specific mutation of the method according to claim 1.

56.1 Paragraph [0276] on page 60, lines 43 to 51 of the patent in suit states that the mutation 185delAG -> ter39 is a predisposing mutation that is relatively common, occurring in 12 % of the probands studied. The same paragraph further states that "[m]any of the probands screened to date for BRCA1 mutations were selected for having a high prior probability of having such mutations. Thus the mutations found in this set may not be representative of those which would be identified in other sets of patients. However, the two most frequent BRCA1 mutations (5382 ins C and 185 del AG) have been found multiple times in targeted screening in sets of probands who were either unselected for family history or ascertained with minimal family history." The patent in suit discloses that the mutation 185delAG -> ter39 occurs at a

relatively high frequency and thus allows effective screening of a human subject.

56.2 Opponents have argued that according to the post-published document D29, the mutation 185delAG -> ter39 was only predominant in people of Ashkenazi Jewish descent, and could not generally be considered as a particularly frequent mutation. Since the high frequency of the mutation in the Ashkenazi Jewish population was not disclosed in the patent in suit, this advantageous property could not be used in the formulation of the technical problem or support the acknowledgment of an inventive step.

56.3 The Board agrees that the high frequency of the mutation 185delAG -> ter39 in the Ashkenazi Jewish population, which is not disclosed in the patent in suit, cannot support the finding that the technical problem has been solved. However, the Board takes the position that on the basis of the evidence on file, in particular document D100, a declaration of Dr Critchfield, the mutation 185delAG -> ter39 is to be considered as a frequent mutation also with respect to the general population. According to document D100, the frequency of the mutation 185delAG -> ter39 was 8.92 % in samples of Ashkenazi ancestry analyzed for mutations in BRCA1 at Myriad (see page 3, point 6), and 0.47 % in non-Ashkenazi samples (see page 3, point 8). It is further stated in point 8 of this document that "[o]ther than the **185delAG** and 5385insC mutations, the mutation with the highest frequency in the non-Ashkenazi samples analyzed at Myriad is the C61G mutation with a frequency of **0.30%**. Thus, the **185delAG** mutations is **1.6** times more prevalent than the C61G

mutation among the **non-Ashkenazi** samples analyzed at Myriad". The Board concludes from this data that although the mutation 185delAG -> ter39 is considerably less frequent in non-Ashkenazi samples when compared to samples from people of Ashkenazi ancestry, the mutation is to be considered as a frequent one also in people who are not of Ashkenazi descent. Document D100 thus supports the statement in the patent in suit that the mutation 185delAG -> ter39 is a frequent one and thus allows effective screening.

56.4 Opponents have furthermore argued that the technical problem had not been solved over the whole scope of the claims, because the frequency of the mutation 185delAG -> ter39 varied dramatically from country to country, as evidenced by document D119 which gives an overview of BRCA1 mutation spectra in different European countries. This document showed that the frequency of the mutation 185delAG -> ter39 is relatively high in some countries, for instance in Spain (15 %) and in the United Kingdom (19 %), but very low in other European countries including Italy, Belgium, Germany, Switzerland and Austria. With respect to these latter countries, screening for the mutation 185delAG -> ter39 would not be useful and in no way cost-effective. An advantageous effect thus only existed for a very limited part of the human population, and not over the whole scope of the claim.

56.5 The Board cannot follow this line of argument since although the mutation 185delAG -> ter39 occurs less frequently in some countries than in others, this cannot prejudice the fact that this mutation is a frequent one in the general human population.

Furthermore, the determination of the presence of said mutation in the BRCA1 gene of a human subject according to the method of claim 1 would always allow the diagnosis of a predisposition for breast and ovarian cancer, irrespective of the country from which the human subject originates.

57. The relevant question for assessing inventive step is whether or not, at the fourth priority date, the provision of a diagnostic method for finding the mutation 185delAG -> ter39 would have been obvious for a skilled person faced with the problem posed.

58. The Board agrees with the Opponents and Appellant I that the skilled person in the present case would be a team of experts including at least a molecular geneticist and a medical doctor having access to patient samples.

59. It has been pointed out in a number of decisions of the Boards of Appeal in the technical field of bio-technology that, in evaluating the attitude of the skilled person, one should not confuse the "hope to succeed", which is linked to the wish that a result be achieved, with the "reasonable expectation of success", which is linked to the ability to reasonably predict, based on the particular technical circumstances, a successful conclusion of the project within acceptable time limits (see decisions T 296/93 of 28 July 1994, point (7.4.4), T 923/92 of 8 November 1995, point (51), T 223/96 of 29 January 1999, point (23) and T 1213/05, supra, point (77)). In this respect, each case has to be assessed on its own merits, and any hindsight has to be avoided.

60. The Board notes that from the content of document D1, there was still a considerable degree of uncertainty with respect to the mutations that predispose individuals to BRCA1-linked breast and ovarian cancer and to the development of BRCA1 screening methods. Although at the time of its publication, the document was seen by the scientific community as disclosing the identification of the BRCA1 gene, the authors of the document themselves expressed some caution in this regard by giving their publication the title "A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene BRCA1". At the end of document D1 (page 71, column 1, paragraph 1), it is stated: "The large size and fragmented nature of the coding sequence will make exhaustive searches for new mutations challenging. Nevertheless, the percentage of total breast and ovarian cancer caused by mutant BRCA1 alleles will soon be estimated, and individual mutation frequencies and penetrances may be established. This in turn may permit accurate genetic screening for predisposition to a common, deadly disease."

The Board furthermore observes that document D1 does not give any information on the frequencies of the mutant alleles listed in Table 2 in BRCA1 predisposed individuals. It was found out only later, i.e. after the fourth priority date, that the mutation indicated in Table 2 as occurring in kindred 1910 is a relatively frequent mutation (see the comments on mutation "5385insC" in document D100).

61. The Board considers that the skilled person, departing from the disclosure of document D1, would have readily undertaken to identify BRCA1 predisposing mutations

suitable for effective screening in the hope to succeed. This hope is expressed also by the authors of the document by stating in the above quoted passage that "the percentage of total breast and ovarian cancer caused by mutant BRCA1 alleles will soon be estimated, and individual mutation frequencies and penetrances may be established". However, in the same paragraph, the authors of document D1 describe the task of carrying out exhaustive searches for new mutations as being "challenging", in view of the large size and fragmented nature of the coding sequence. The Board is therefore convinced that, in view of the disclosure in document D1, the skilled person, taking a conservative attitude, would not have reasonably expected to successfully identify a mutation that allows the development of an effective screening for inherited breast and ovarian cancer within acceptable time limits. From the skilled person's perspective at the fourth priority date of the patent in suit, finding such a mutation would not only involve a substantial amount of "challenging" work, but would also require a "lucky strike", which could in no way be predicted on the basis of document D1.

62. Opponents have argued that finding the mutation 185delAG -> ter39 was obvious because, starting from document D1, the skilled person would immediately have carried out an extensive screening of the available patient samples and, by doing so, would have inevitably arrived at said mutation. This was evidenced by the fact that the well-documented families "BOV3" known from document D9 (also mentioned in post-published document D5, Table 3) and "2979" known from document

D42 - access to these families was available at the fourth priority date - contained the mutation 185delAG -> ter39, as confirmed by document D47. By following the suggestion in document D1 to find mutations, catalogue them and determine their frequencies, the skilled person would also have obtained the information of the frequency of the mutation 185delAG -> ter39. Also, the more frequent a mutation was, the higher was the chance to find it. To carry out the screening involved nothing but repetitive work, which would have inevitably resulted in the claimed invention. The finding of the mutation 185delAG -> ter39 was thus a "one-way street" situation, not a lucky strike. This was also supported by the post-published document D96, which stated that within days after the disclosure of the complete nucleotide sequence of BRCA1 in GenBank, oligonucleotide primers had been prepared to start the genetic analysis, and that less than a week later, some groups had already found sequence changes in their own patient samples (see column 1, last paragraph of the document).

63. The Board cannot follow this line of argument as it is based on an *ex post facto* analysis, which should be avoided in the assessment of inventive step (see Case Law of the Boards of Appeal of the European Patent Office, 5th edition 2006, chapter I.D.5.). It is only with the benefit of hindsight that one can now know what the skilled person would have had to do at the relevant time in order to arrive at the claimed subject-matter. This does, however, not reflect the skilled person's circumstances at the fourth priority date, which should not be confused with the circumstances of those scientists that, in the hope to

succeed, eagerly undertook the "challenging" search for BRCA1 predisposing mutations and, by doing so, might have arrived at the claimed invention.

64. Opponents have further argued that the claimed subject-matter was obvious over a combination of documents D1, D115 and D117. Document D115 disclosed that a familial aggregation of ovarian cancer occurs in the Israeli Jewish population, and the skilled person would have considered this population as a suitable group for BRCA1 mutation analysis in order to find further predisposing mutations. Upon screening these Israeli Jewish women, the skilled person would inevitably have identified 185delAG -> ter39 as a predisposing mutation. This was evidenced by the post-published document D116 which showed that said mutation was detected in 38.9 % of ovarian cancer patients with familial history and 13.1 % of family history-negative ovarian cancer cases in this population (see abstract, section results). Although document D115 did not mention the term "BRCA1", there would have been no doubt for the skilled person that said population was appropriate for the further screening for BRCA1 mutations, because it was known from document D117 that the BRCA2 gene was linked to susceptibility to hereditary breast cancer only, i.e. not ovarian cancer.

65. The Board considers that the Opponents' argumentation is again based on an *ex post facto* analysis and that in the absence of a reasonable expectation of success (see points 59 to 61 above), the skilled person would not have undertaken the screening of the population of document D115.

66. Opponents have also argued that the detection of the mutation 185delAG -> ter39 was made easy by the disclosure of the mutation 188del11 in document D1 in view of the proximity of the two mutations in exon 2.

67. However, in the Board's judgment, the skilled person could not expect from the disclosure of the mutation 188del11 in document D1 to find a further predisposing mutation in this area of exon 2, let alone a mutation that would allow effective screening. Therefore, the Opponents' argument fails.

68. Opponents have further argued that document D6 disclosing the mutation 185delAG -> ter39 had been submitted for publication on 3 November 1994 (as was indicated on the last page of the document), thus shortly after the publication of document D1. According to the Opponents, this demonstrated that it had not been difficult to identify the mutation.

69. The Board cannot see how the submission for publication of the mutation 185delAG -> ter39 in document D6 (the authors of which include three of the inventors of the patent in suit) shortly after the publication of document D1 could in any way prejudice the inventiveness of claim 1. The Board takes the position that, in view of what has been said points at (54) to (67) above, it is only with the benefit of hindsight that one could conclude that it would have been straightforward to arrive at the claimed invention.

70. In view of the above considerations, the subject-matter of claim 1 is considered to involve an inventive step. Since claim 2 also requires the determination of the

mutation 185delAG -> ter39 in the claimed method, the reasons given above as to why the subject-matter of claim 1 involves an inventive step apply analogously also for the subject-matter of claim 2. Claims 3 to 5 are dependent on claims 1 and 2 and their subject-matter thus likewise involves an inventive step. The nucleic acid probe of claim 7 is considered to involve an inventive step because it must contain the mutation 185delAG -> ter39. The same applies to the replicative cloning vector of claim 8 comprising an isolated nucleic acid according to claim 7, and to the host cells of claim 9 which are in vitro transformed with a vector of claim 8.

Consequently, the subject-matter of claims 1 to 9 fulfils the requirements of Article 56 EPC.

Sufficiency of disclosure (Article 83 EPC)

71. The Opposition Division decided in point (14) of the appealed decision that the patent disclosed a method for diagnosing a predisposition for breast and ovarian cancer based on the determination of the mutation 185delAG -> ter39 in a manner sufficiently clear and complete for it to be carried out by a skilled person.

72. None of the Opponents has submitted any evidence or argument to further substantiate this issue during the present appeal proceedings.

73. The Board, having no reason to deviate from the decision taken by the Opposition Division in this respect, decides that the requirements of Article 83 EPC are met.

Patentable invention (Article 52(2) EPC)

74. In the notice of opposition, dated 22 February 2002, Opponent 06 argued that the sequences of the probes according to present claim 7 occur in nature and are therefore a discovery rather than an invention. In view of Article 52(2) EPC, said probes were thus not patentable. During the oral proceedings, this point was not further pursued by any of the Opponents.

75. According to the case law of the Boards of Appeal (see decision T 272/95 of 23 October 2002), Article 52(2)(a) EPC is to be interpreted in accordance with the implementing Rule 29(2) EPC (corresponding to Rule 23e(2) EPC 1973) which states:

"(2) An element isolated from the human body or otherwise produced by means of a technical process including the sequence or partial sequence of a gene may constitute a patentable invention, even if the structure of that element is identical to that of a natural element".

76. Claims 7 relates to a nucleic acid **probe** comprising partial DNA sequences of the human BRCA1 gene, which is described in the patent in suit as having been obtained by technical processes. This probe is thus an isolated element of the human body as defined in Rule 29(2) EPC and thus patentable subject-matter. Accordingly, the subject-matter of claim 7 does not fall within the category of inventions which may not be patentable as being discoveries (Article 52(2)(a) EPC).

Exceptions to patentability (Article 53(a) and (c) EPC)

77. Opponent 04 in the notice of opposition, dated 25 February 2002, and Opponent 06 argued that methods for diagnosing a predisposition for breast and ovarian cancer or for diagnosing a breast or ovarian lesion for neoplasia in/of a human subject should not be regarded as patentable invention according to Article 52(4) EPC 1973 (now Article 53(c) EPC). During the oral proceedings, this point was not further pursued by any of the Opponents.

78. Article 53(c) EPC (which corresponds to Article 52(4) EPC 1973) states that European patents shall not be granted in respect of methods for treatment of the human or animal body by surgery or therapy and diagnostic methods **practised on the human or animal body.**

The Enlarged Board of Appeal in its Opinion G 1/04 (OJ EPO 2006, 334) said that Article 52(4) EPC 1973 excludes diagnostic methods practised on the human or animal body only if the method steps of technical nature belonging to the preceding steps which are constitutive for making a diagnosis as an intellectual exercise are performed on a living human or animal body (see point (6) of the reasons).

79. According to present claims 1 to 6, all method steps of technical nature are performed on a tissue sample of a human subject. The Opponents' argument must therefore fail. The claims do not refer to subject-matter not patentable according to Article 53 (c) EPC (Article 52(4) EPC 1973).

80. Furthermore, Opponent 04 argued that the subject-matter of the claims contravened the requirements of Article 53(a) EPC. If the patent was granted, patients were no longer able to have their genetic information read and interpreted by the organisation of their choice and it could not be guaranteed that criminal and medical gene databases were kept strictly separate, which was an accepted ethical principle in the member states of the EPO.

81. Opponent 06 argued that the socio-economic consequences of the patenting of the claimed subject-matter should be considered by the Board under Article 53(a) EPC, because in the present case, these consequences touched ethical issues. Patenting of the claimed subject-matter would not only result in increased costs for patients, but would also influence the way in which diagnosis and research would be organized in Europe, which would be clearly to the detriment of patients and doctors. The fact that a particular group of patients, i.e. patients suspected to carry a predisposition to breast cancer, would be faced with severe disadvantages and would become dependent on the patent proprietor, was contrary to human dignity. Therefore, the claimed subject-matter constituted an exception to patentability under Article 53(a) EPC.

A further indication that the legislator intended to enforce a critical examination of this aspect was seen in the transfer of Article 52(4) EPC 1973 to Article 53 EPC, referring to exceptions to patentability.

82. This Board, in a different composition, already in decision T 1213/05 (supra) has dealt with the socio-

economic and ethical consequences of the patenting of diagnostic methods involving the use of human genetic material.

The Board in the present composition follows decision T 1213/05 (supra, see especially points (52) and (53)) and, on this basis, rejects Opponents' objection under Article 53(a) EPC.

Industrial applicability (Article 57 EPC)

83. Claim 7 refers to a nucleic acid probe defined by a nucleotide sequence.

According to Appellants II to IV the possible uses of such probes were not industrial applications in the sense of Article 57 EPC in connection with Rule 29(3) EPC, which required that, with regard to inventions concerning the human body and its elements, the industrial application of a sequence or a partial sequence must be disclosed in the patent application.

The capacity of a single stranded DNA sequence to hybridize with a complementary single-stranded sequence was a consequence of the physico-chemical properties of each single-stranded DNA molecule and was thus a universal characteristic thereof. Such universal characteristic could not be accepted as a basis for an industrial application within the meaning of Article 57 and Rule 29(3) EPC.

During the oral proceedings, this point was not further pursued by any of the Opponents.

84. This Board, in a different composition, already in decision T 1213/05 (supra, see especially point (62)) has dealt with the industrial applicability of nucleic acid probes.

The Board found, and the present Board agrees with this position, that the provision of a probe useful in a diagnostic method cannot be considered to be merely a research tool for the detection of complementary single stranded DNA molecules, but that such probe can also be commercially applied for a diagnostic purpose, in the present case to detect the presence of a BRCA1 allele predisposing an individual to cancer.

85. Accordingly, the requirements of Article 57 EPC are met.

Adaptation of description

86. The description has been correctly adapted to the subject-matter of claims 1 to 9.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent in the following version:

Description: Pages 3, 3a, 4 to 24 and 138 submitted at the oral proceedings on 13 November 2008; pages 25 to 137 of the patent specification as granted.

Claims: 1 to 9 of the main request, filed with a letter dated 2 June 2008.

Figures: 1 to 10 on pages 151 to 169 of the patent specification as granted.

The Registrar: The Chair:

P. Cremona U. Kinkeldey