EXHIBIT E

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Date: 17-07-2009

Reference	Application No./Patent No.
OPPO 06	95305605.8 - 2405 / 0705903

Applicant/Proprietor: The University of Utah Research Foundation

Decision to maintain the European patent in amended form (Art. 101(3)(a) EPC)

European Patent No. : **0705903**
Filing date : 11.08.95
Priority claimed : 12.08.94/ USA 289221
02.09.94/ USA 300266
16.09.94/ USA 308104
29.11.94/ USA 348824
24.03.95/ USA 409305
07.06.95/ USA 480784
07.06.95/ USA 483553

Designated States and
Patent proprietor(s) : AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
The University of Utah Research Foundation
615 Arapeen Drive, Suite 310
Salt Lake City,
Utah 84108/US

is maintained as amended.

Registered letter
EPO Form 2329 12.07 10.07.09

to EPO postal service: 10.07.09

Maintenance is based on the documents as specified and notified previously.

The announcement that the European patent is being maintained as amended will be published in the European Patent Bulletin 09/33 on 12.08.09.

Your attention is drawn to the communication of 16.03.09, regarding the requirements and time limits for submitting translations of the new European Patent Specification in the designated Contracting States.

Opposition division

1st Examiner:	2nd Examiner:	Chairman:	Legally qualified member:
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Datum/Date 09.06.05

Zeichen/Ref./Réf.	Anmeldung Nr./Application No./Demande n°./Patent Nr./Patent No./Brevet n°.
K27090PP(EP)S3	95305605.8-2405/0705903

Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire
THE UNIVERSITY OF UTAH RESEARCH FOUNDATION

INTERLOCUTORY DECISION IN OPPOSITION PROCEEDINGS (ARTICLES 102(3) AND 106(3) EPC)

The Opposition Division - at the oral proceedings dated 24./25.01.05
- has decided:

Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the Convention.
[ ] Additional decision:

The reasons for the decision together with Form 2339 relating to the documents on which it is based are enclosed.

POSSIBILITY OF APPEAL:
This decision is open to appeal. Attention is drawn to the attached text of Articles 106 to 108 EPC.

OPPOSITION DIVISION:

ISERT B Chairman	STOLZ B 1st Examiner
SPRINKS M T 2nd Examiner	TREICHEL P E Legally qualified examiner

Enclosures: Reasons for the decision (Form 2916, 16 pages)
Text of Articles 106-108 EPC (Form 2019)
Documents relating to the amended text (Form 2339.4)
[ ] Minutes of oral proceedings

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Zeichen/Ref./Réf.	Anmeldung Nr./Application No./Demande n°./Patent Nr./Patent No./Brevet n°.
E18565-BF OPPO 01-03	95305605.8-2405/0705903

Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire
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Datum/Date

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

INTERLOCUTORY DECISION IN OPPOSITION PROCEEDINGS (ARTICLE 106(3) EPC)

The Opposition Division - at the oral proceedings dated 24., 25.01.05
- has decided:

Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the Convention.
[ ] Additional decision:

The reasons for the decision together with Form 2339 relating to the documents on which it is based are enclosed.

POSSIBILITY OF APPEAL:
This decision is open to appeal. Attention is drawn to the attached text of Articles 106 to 108 EPC.

OPPOSITION DIVISION:

ISERT B Chairman	STOLZ B 1st Examiner
SPRINKS M T 2nd Examiner	TREICHEL P E Legally qualified examiner

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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

INTERLOCUTORY DECISION IN OPPOSITION PROCEEDINGS (ARTICLE 106(3) EPC)

The Opposition Division - at the oral proceedings dated 24.25.01.05
- has decided:

Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the Convention.
[ ] Additional decision:

The reasons for the decision together with Form 2339 relating to the documents on which it is based are enclosed.

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Datum/Date
09.06.05

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
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The Opposition Division - at the oral proceedings dated 24./25.01.05
- has decided:

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[ ] Additional decision:

The reasons for the decision together with Form 2339 relating to the documents on which it is based are enclosed.

POSSIBILITY OF APPEAL:
This decision is open to appeal. Attention is drawn to the attached text of Articles 106 to 108 EPC.

OPPOSITION DIVISION:

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[ ] Minutes of oral proceedings

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95305605.8	IDOP			

Facts and Submissions

1. European Patent No. 705903 is based on European Patent application No. 95305605. The filing date is 11.08.1995. Mention of the grant was published on 23.05.2001 in Bulletin 2001/21.

2. Oppositions have been filed by the following parties and on the following dates:

O1:	Institut Curie, Paris, France	22.02.2002
O2:	Assistance Publique, Hopitaux de Paris, France	22.02.2002
O3:	Institut Gustave Roussy, Villejuif, France	22.02.2002
O4:	Vereniging van Stichtingen Klinische Genetica Leiden, The Netherlands, et al.	25.02.2002
O5:	De Staat der Nederlanden	22.02.2002
O6:	Greenpeace e.V., Hamburg, Deutschland	22.02.2002

Oppositions were filed under Art. 100(a), 100(b) and 100(c) EPC, i.e. for lack of novelty (Art.54 EPC), inventive step (Art. 56 EPC), non-patentability of subject matter (Art. 52(2) EPC), lack of industrial applicability (Art. 57 EPC), insufficiency of disclosure (Art. 83 EPC), and extension of scope (Art. 123(2) EPC). In support of the submissions by the opponents, a large number of documents has been cited.

All opponents requested revocation of the patent in its entirety.

3. In a letter dated 10.12.2002, the Patentee (P) presented his position and submitted a new set of claims as well as several documents. He presented a consolidated list of the documents cited (D1-D97) (the list, including also later filed documents, is shown as Annex). He requested maintenance of the patent on the basis of the new set of claims.

4. Third party observations (Art. 115 EPC) were filed on 24.02.2003. Their contents appeared however to be directed to the copending opposition against EP 705902. The submissions went in any case not beyond the submissions already filed by other opposing parties.

5. A summons to attend oral proceedings together with a preliminary opinion of the

Opposition Division (OD) was issued on 26.04.04. The deadline for written submissions was set to 24.11.2004.

6. With letter dated 20.10.2004, the P requested postponement of the oral proceedings or as an auxiliary measure to set the deadline for written submissions to 24.12.2004. The OD did not follow this request (cf. communication of 09.11.2004).

7. In a letter dated 24.11.2004, the P filed a new main and three auxiliary requests as well as documents D98 to D100.
In a letter dated 24.11.2004, O4 submitted further observations as well as documents D101 to D107.

8. Oral proceedings were held on 24 and 25 January, 2005, during which a new auxiliary request I was submitted. Pending auxiliary requests 1 to 3 were renumbered as 2 to 4. Furthermore, during the proceedings a new auxiliary request 3 was filed which replaced pending and renumbered auxiliary request 3. The P also filed D108 (shown as Annex), which was admitted into the proceedings.

   In view of the late filing, the OD exerted its discretion under Art. 114(2) EPC not to admit Auxiliary request 1.

9. At the end of the proceedings the OD announced its interlocutory decision to maintain the patent on the basis of auxiliary request 3 and the description as amended during the proceedings.

Reasons for the decision

10. The oppositions filed by all parties are admissible. The requirements of Art. 99(1) and Art. 100 EPC, and of R. 1(1) and R. 55 EPC, are met.

11. The main request

    Claim 1 of the main request is directed to: a method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is a germline alteration in the sequence of the BRCA1

gene in a tissue sample of said subject compared to the nucleotide sequence set forth in SEQ ID No: 1 or a wild-type allelic variant thereof, said alteration indicating a predisposition to said cancer being 185delAG->ter39.

Independent claim 6 is directed to: a nucleic acid probe having 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG->ter39.

12. Art. 123(2,3) EPC

12.1 The opponents held that the mutation referred to in claim 1 represented an arbitrary selection of a particular mutation from among many mutations listed in Tables 12, 12A and 14 of the application as originally filed, and they did not see a basis for this selection. Also, the term "SEQ ID NO: 1 or a wild-type allelic variant" was submitted to have no basis in the original disclosure, let alone a method combining all the features of claim 1. As for claim 6, it was submitted that the range of 15 to 30 nucleotides of SEQ ID NO: 1 was without basis.

12.2 The OD regards claim 17 of the application document as the most obvious basis for new claim 1. This claim is literally identical in wording except for the last half sentence specifying the mutation. Instead of referring literally to 185delAG->ter39, the originally filed claim reads: said alterations indicating a predisposition to said cancer being selected from the mutations set forth in Tables 12, 12A and 14. The reference in claim 1 to Table 14 (and to the other Tables) is a clear and unambiguous reference to the many mutations listed therein. This reference represents the most concise form of referring to the specific mutations. Thus, the claim as originally filed is directed to methods of diagnosing a predisposition for breast and ovarian cancer by essentially determining if <u>any</u> of the mutations individually listed in said Tables is present. Since 185delAG->ter39 is the second mutation of Table 14, claim 17 as originally filed clearly and unambiguously disclosed a method of diagnosing a predisposition to breast and ovarian cancer which comprised determining if the alteration was 185delAG->ter. The OD agrees therefore with the P that claim 1 meets the requirements of Art. 123(2) EPC. Since independent claims 1 and 2 are derived from claims 16 and 17 as granted by simply deleting all mutations but the 185delAG->ter39, there can be no extension of scope (Art. 123(3) EPC).

12.3 As for the range of 15 to 30 nucleotides of claim 6, there was agreement among

all parties that there is no explicit disclosure. The OD regards originally filed claim 4 in combination with the definition of probes (pp.14/15) as sufficient basis.
Original claim 4 is directed to a nucleic acid probe wherein the nucleotide sequence is a portion of a nucleic acid encoded by SEQ ID NO: 1 including a mutation from the list set forth i.a. in Table 14. Thus, original claim 4 covers probes, i.e. portions of SEQ ID NO: 1, including the 185delAG mutation.
According to p. 15, lines 8-9, the probes may be short, e.g. in the range of about 8-30 base pairs, and furthermore according to p. 15, lines 22-23, at least about 15 nucleotides and fewer than about 6 kb. There are furthermore indications that short probes, i.e. the lower end of the range of 15-6000 bps are of special interest. The passages are: p. 11, line 14, describing probes as oligomers of about 30 nucleotides in length; p. 14, lines 19-22, describing probes as comprising at least 15 nucleotides, more usually about 7-15 codons (21 to 45 bps) and most preferably about 35 codons (105 bps).
Following T17/85, the instant application documents disclose a minimal value of 15 nucleotides (p. 14, line 19) within the broader range of 8 to 30 nucleotides (p. 15, lines 8-9), and an upper limit of 30 nucleotides of said broader range, hence it also discloses the range from this minimal value of 15 to the upper limit of 30 nucleotides. A similar argument can be made starting from the range of 15 to 6000 bps. According to p. 11, probes can be of 30 nucleotides in length. In combination with the statement that 30 can be the upper limit (of 8 to 30), the description discloses the range of 15 to 30 bps.
A shorter explanation of the same fact is that the disclosure of two overlapping ranges, i.e. 8 to 30 and 15 to 6000, respectively, also discloses the range of overlap, i.e. 15 to 30.
The OD is therefore of the opinion that the claimed range of 15 to 30 nucleotides is directly and unambiguously derivable from the application as filed. Thus, claim 3 meets the requirements of Art. 123(2) EPC.

Claim 3 as granted was directed to nucleic acid probes where the nucleotide sequence is a portion of a sequence which is SEQ ID 1 and contains a mutation as defined in claim 1. The 185delAG->ter39 mutation is the second mutation in claim 1. Claim 3 as granted contained no limitation of the length of the probes.
Claim 6 of the main request is directed to probes of 15 to 30 nucleotides in length comprising the 185delAG->ter39 mutation. The size range of the claimed probes is thus narrower than the range of the probes in claim 3 as granted. Hence, there is no contravention of Art. 123(3) EPC.

13. Art. 84 EPC

13.1 The Opponents submitted that the expression "wild-type allelic variant" lacked clarity in the absence of a definition of the function of the disclosed BRCA1 protein.

13.2 First, the OD is of the opinion that this expression was already present in claim 16 as granted and is therefore under formal aspects (Art. 84 EPC; T301/87) not open to an objection.
Second, even if the term were open to an objection, the OD is of the opinion that it is clear in the light of the patent specification. On p. 12, line 7, it is stated that individuals with the wild-type BRCA1 gene do not have cancer resulting from the BRCA1 allele. On p. 13, line 37, it is stated that the term BRCA1 allele refers to normal alleles as well as to alleles carrying variations that predispose individuals to develop cancer. Normal alleles and wild-type alleles are in this context synonymous. In the present context, it is therefore clear that the method of claim 1 requires comparison of a patient sequence with SEQ ID NO: 1 or an allelic variant which does not contain an alteration predisposing to cancer.

14. Art. 83 EPC

14.1 The Opponents submitted in essence that the method of claim 1 left the term "wild-type allelic variant" open to interpretation to such an extent that the person of skill could not know if there was a predisposition to cancer or not. Also, at the time of filing, there were insufficient data to allow the person of skill to draw a conclusion about the importance of the mutation.

14.2 In this context, the P submitted D108 to demonstrate that the mutation 185delAG ->ter39 was routinely assayed.

14.3 The OD is of the opinion that the latter objection relating to the availability of sufficient statistical data is in essence an objection under Art. 84 EPC for lack of support by the description. But even if one were to admit the objection, the OD considered the data on file sufficient. The mutation 185delAG has been found in several families (cf. Tables 14, 15) and is regarded as relatively common (p. 60, line 52 of the application as published). The conclusion in this paragraph is cautious in view of the fact that the tested families and the mutants found may not

be representative for other sets of patients. The final statement points however out, that the 185delAG mutation is also found in probands with minimal or no family history. The OD considers these statements sufficient to support claim 1. As to the objection that the method cannot be carried out by the person of skill (Art. 83 EPC), the OD is of the opinion that the description provides sufficient structural information about the BRCA1 gene in order to perform the method of claim 1. The essential feature of the method is the detection of the deletion of an A and a G at positions 185/186 of SEQ ID No: 1 or at the corresponding position of a wild-type allelic variant. The complete structure of the BRCA1 gene as well as several ways of testing for the deletion are mentioned (SEQ ID No: 1; p. 10 of the application document). From D108 it can be taken that this deletion is routinely tested for, and none of the cited documents mentions any technical difficulties in assessing the deletion. The OD agrees with the P, that the requirements of Art. 83 EPC are met.

15. Priority

15.1 The final sequence of the BRCA1 gene as defined in SEQ ID No: 1 is for the first time disclosed in P5 (US409305). The Opponents submitted in essence that the subject matter of claim 1 was defined by reference to SEQ ID NO: 1 and was therefore entitled to a priority date of 24.03.1995 (P5).

15.2 The P considered the subject matter to be disclosed in the priority application of 29.11.1994 (P4, US348824) because the essential feature of the claim was deletion of nucleotides AG at position 185/186. This could be found in Tables 14 and 15 of P4. The few differences in SEQ ID NO: 1 were not crucial.

15.3 The OD disagrees with the P's view that SEQ ID NO: 1 is a technical feature which is not related to the function and effect of the invention. In the P's submission, the function to be tested is the deletion at positions 185/186 while the remainder of the sequence is of less importance and should therefore be allowed to vary.
According to decision G 2/98 (OJ EPO 2001, 413), the requirement for claiming priority of 'the same invention', referred to in Article 87(1) EPC, means that 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 (cf. decision G 2/98, point 9 of the reasons).
Furthermore, according to G 2/98 the concept of the same invention must be given a narrow or strict interpretation equating it with the concept of the same subject-matter. An extensive or broad interpretation making a distinction between technical features which are related to the function and effect of the invention and technical features which are not, with the possible consequence that a claimed invention is considered to remain the same even though a feature is modified or deleted, or a further feature is added, is inappropriate and prejudicial to a proper exercise of priority rights.
The OD considers Seq ID 1 to constitute an essential feature of claim 1. The claim is directed to a method of determining whether there is a germline alteration in a BRCA1 gene compared to SEQ ID NO: 1 or a wild-type allelic variant thereof. SEQ ID NO: 1 is thus not only the reference sequence for the assessment of whether there is a deletion at positions 185/186 or not but also the reference sequence for the definition of wild-type allelic variants. Hence, it is essential. Since the exact sequence of SEQ ID NO: 1 has been disclosed in P5, the claim has basis in said priority application.

16. Art. 54 EPC

16.1 Documents D5 and D6 were both published before the filing date of P5. For the purpose of identifying the mutations, both documents refer to the BRCA1 sequence deposited at Genbank under accession number U14680 (D5, Table 3; D6, p. 398, left column) and available to the public since October 8, 1994. At least as far as the numbering is concerned, this sequence matches Seq ID No: 1 of P5. Thus, there is no doubt that both documents refer to the same 185delAG mutation as the instant application (D5, Table 3; D6, Table 3). In both documents del185AG ->ter39 is identified as one of the relatively common mutations (D5, p. 395, 1st paragraph; D6, p. 539, right hand column, "frequency of recurrent mutations"). In these documents, the method of detecting the 185delAG mutation has not been applied to the diagnosis of a predisposition to breast or ovarian cancer but rather to the assessment of the genetic status of affected patients. Thus, there is no explicit disclosure of the diagnostic method of claims 1 or 2. However, both documents conclude with a suggestion that screening for these recurrent mutations could lead to a relatively simple diagnostic test (D5, abstract, "Conclusions") or that screening for BRCA1 mutations in high risk woman could

be facilitated if common mutations are sought first (D6, p. 396, right hand column). Thus, D5 directly suggests to use a screen for the presence of the 185del->AG mutation in a diagnostic test. Taking into consideration the whole context of these documents, the OD considers the concluding remarks of both documents to anticipate the subject matter of claims 1 and 2.
Consequently, the main request lacks novelty (Art. 54(2) EPC).

17. Auxiliary Request 1

17.1 This request was submitted at the oral proceedings.
Claims 1 and 2 of this request differ from the main request in that the reference to Seq ID 1 and allelic variants thereof was replaced by a reference to GenBank accession number U-14680 of October 8, 1994.

As a basis for this element, the P referred to p. 43, line 7, of the application document and to the corresponding passage on p. 74, line 18, of P4.
As a reason for the late filing, the P mentioned that this amendment had only come to his mind after the oral proceedings of a related case, the week before, had shown that Auxiliary request 1 as filed with letter of 24.11.2004 would probably not overcome the objections of the Os. The P also submitted that the deposited sequence U-14680 had been cited as novelty destroying and that therefore the opponents were familiar with this item.

17.2 The opponents strongly objected to the admission of this new request because the amendment was completely unexpected and led to new problems under Art. 123(2,3) EPC, Art. 84 EPC, and Art. 87 EPC.

17.3 It is the ODs opinion that Auxiliary request 1 is inadmissible at this stage of the proceedings. Since the main request has been maintained, it is an additional request, which was filed at the latest possible moment (during oral proceedings) and therefore only allowable under specific circumstances (cf. e.g. T 153/85, T 648/96, T 794/94). The criteria for admissibility have been developed for proceedings before the Boards of Appeal but were also held to apply to opposition proceedings (T 648/96, pt. 2.2).
A prerequisite is clear admissibility in order to avoid undue delay or interruption of the proceedings (T 406/86, pt. 3.2; T 648/96, pt. 2.2; T 794/94, pt. 2.1).
New claims 1 and 2 define the reference sequence used for diagnosing a

predisposition to breast or ovarian cancer by reference to a sequence deposited at GenBank under accession number U-14680 at October 8, 1994. Thus, a feature from the description has been introduced into the claim. Up to this point of the proceedings, it was the P's position (cf. P's submissions in Annex III, pp. 13-15, of 10.12.2002), that the sequence deposited as U-14680 at October 8, 1994 was different from SEQ ID NO: 1 of the granted claims. Therefore, the OD agrees with the Os that this is a completely unexpected submission comprising new subject matter. They can therefore not be reasonably expected to be prepared for this case.

Moreover, the proposed amendments would only be admissible if they were clearly allowable (e.g. T 631/92, pt. 2.1). However, a preliminary analysis under Art. 123(2,3) and Art. 84 EPC reveals that the claims are not clearly allowable. The description contains a reference to U-14680 but does not mention a date of October 8, 1994. Thus, there is possibly no basis for this feature of the claims (Art. 123(2) EPC). As long as the exact history of U-14680 has not been established, it is furthermore open, if the shift from Seq ID 1 to U-14680 as a reference sequence would lead to an extension or shift of the scope of protection (Art. 123(3) EPC).

Introduction of a reference to a DNA sequence in an external database is also inadequate to define the subject matter in a claim. The sequence of U-14680 is not disclosed in any part of the patent application or the patent specification. Defining the claimed subject matter in this way does not put the person of skill into a position of establishing the scope of protection on the basis of the patent specification alone. Hence, the claims are not clear (Art. 84 EPC).

In view of these new, unresolved issues, the OD does not consider Auxiliary request 1 to be clearly allowable under Articles 123(2,3) and 84 EPC. Furthermore, in view of the fact that priority has been an issue from the beginning of opposition proceedings, the OD does not accept P's reasons for the late submission. It therefore exercises its discretion under Art. 114(2) EPC not to admit Auxiliary Request 1.

18. Auxiliary Request 2

Basically, the first claim is directed to a method for diagnosing a predisposition for breast or ovarian cancer comprising the detection of a germline alteration defined as the deletion of AG in a position which in turn is defined by reference to a

human BRCA1 gene. This latter BRCA1 gene is defined as being obtainable by cloning it either from a genomic or from a cDNA library (as specified in the claim), and encoding a polypeptide of 1863 amino acids in length, having a molecular weight of 208 kilodaltons, and comprising SEQ ID No: 82.

19. Art. 123(2) EPC, Art. 84 EPC

19.1 The P provided detailed information on the basis of the disclosure of the claimed subject matter in the application document as filed.

19.2 The Opponents regarded the claim as a combination of features which was not directly and unambiguously derivable from the application as filed (mosaicing). Furthermore, it was questioned if a product by process definition should be allowed in a method (process) claim at all. A clarity objection was raised against the feature "208 kilodaltons" because the way of assessing it was unspecified and different results would be obtained depending on the method used.

19.3 The OD takes the view that there is no fundamental problem with using a product by process definition for a reference product in a method claim. This holds true as long as the reference product is unambiguously defined by the specified process(es). The prerequisite is a clear and unambiguous basis in the application documents as filed.

The OD recognizes an unambiguous basis for the subject matter of the first eight lines of claim 1 (cf. above, point 12.2). However, the subsequent specification of the BRCA1 gene lacks basis.

The processes of screening for and isolating the BRCA1 gene from a genomic or a cDNA library produce a family of genes that may differ structurally at various positions. From this family of genes, the definition of claim 1 requires the selection of a subgroup of molecules defined as encoding a BRCA1 protein having 1863 amino acids in length, a molecular weight of 208 kilodaltons and comprising SEQ ID NO: 82 (the zinc finger domain). These latter three elements are all disclosed in Example 8 (p. 42/43 of the application as published), SEQ ID NO: 82 being identical to the sequence of Fig. 5 discussed therein. These features are derived from the specific sequence of SEQ ID NO: 1. But Example 8 does not disclose a family of BRCA1 genes defined by sharing the afore mentioned three features. Example 8 discloses a BRCA1 protein in which not only the segment of SEQ ID NO: 82 is completely specified but also the remainder of the sequence (SEQ ID

NO: 2). Based on this specific sequence of 1863 amino acids, a molecular mass for the protein of SEQ ID NO: 2 of 208 kilodaltons is estimated. The present claim 1 now presents a definition of a BRCA1 gene combining three select features from Example 8 with a generic definition of the BRCA1 gene. The OD considers already this combination of a generic definition with the three specific elements from Example 8 as not directly and unambiguously derivable from the application document.

Moreover, the OD can also not recognize a basis for the definition of the BRCA1 gene as being obtainable by using the probes listed in claim 1. For instance the zinc finger element was nowhere suggested to be useful as a probe, nor is it a likely candidate for a probe. In view of the cited considerable homology (p. 43, line 13) with known domains, it seems more likely that the person of skill would not use probes comprising the zinc finger element. This notion finds support on. p. 45 (line 51) of the application document, where probes were used to detect BRCA1 like sequences in different species under low stringency conditions. These probes specifically lacked the zinc finger domain. The second probe has been used for Northern blots but has also not been suggested to be useful for genomic cloning.
For all these reasons, the OD considers claims 1 and 2 to contravene the requirements of Art. 123(2) EPC.

19.4 The OD agrees with the Os that the feature of "a molecular weight of 208 kilodaltons" is open to interpretation in the absence of an indication how it is determined. The claim is therefore unclear (Art. 84 EPC).

19.5 Auxiliary Request 2 does therefore not meet the requirements of articles 123(2) and 84 EPC.

20. Auxiliary Request 3

Claim 1 is directed to: a nucleic acid probe consisting of 15 to 30 nucleotides of SEQ ID No: 1 and containing the mutation 185delAG->ter39.
Claim 2 is directed to a replicative cloning vector which comprises an isolated nucleic acid according to claim 1 and a replicon operative in a host cell for said vector.
Claim 3 is directed to host cells in vitro transformed with the vector of claim 2.

21. Art. 123(2,3) EPC, Art. 83 EPC, Art. 84 EPC

In view of the OD's opinion about claim 6 of the main request (cf. pt. 12.3 above), the Opponents didn't have any further objections under the cited articles.
The OD cannot recognize any problems under these articles and is therefore satisfied that the respective requirements are met.

22. Priority

The Opponents submitted in essence that claim 1 still contained a reference to SEQ ID NO: 1 which constituted a technical feature of the claim and was therefore only entitled to the priority date of 24.03.1995 (P5).

The OD disagrees with this view. The subject matter of claim 1 is a probe consisting of 15 to 30 nucleotides of SEQ ID NO: 1 and containing the mutation 185delAG->ter39. The subject matter is therefore not the whole of SEQ ID NO: 1 but nucleotide fragments of defined length derived from the segment spanning nucleotides 157 to 214 of SEQ ID NO: 1.
P4 discloses probes, nucleic acid oligomers, each of which contains a region of the BRCA1 gene sequence harboring a known mutation (p. 20, lines 2-3). The 185delAG mutation is disclosed in Table 14 (further support for this can be found in claim 2 of P4). The same passages as in the application document can be found in P4, discussing the length of suitable probes (p. 26, lines 25-26; p. 28, line 17; p. 29, lines 5-7). If one accepts these passages as a basis for a claim to probes of 15 to 30 nucleotides in length (cf. above, point 12.3), then P4 must be seen as disclosing probes of 15 to 30 nucleotides in length covering the 185delAG deletion. This deletion in Table 14 is numbered by reference to sequence U14680, i.e. the deletion is in codons 22 and 23, corresponding to nucleotides 129 and 130 of SEQ ID NO: 1 of P4 (the coding sequence of SEQ ID NO: 1 (P4) begins at nucleotide 64 (p. 106)). Probes of at most 30 nucleotides in length and containing the mutation 185delAG must thus be derived from the nucleotide segment spanning nucleotides 100 to 158 of said SEQ ID NO: 1. Close inspection of this stretch and comparison with the respective stretch of nucleotides of SEQ ID NO: 1 of the application document as filed reveals a complete match. Thus, the subject matter of claim 1 is structurally identical to what was disclosed in P4. Consequently, the OD takes the view that P4 discloses the claimed subject matter in an enabling manner, taking into account the whole

disclosure (G 2/98) and claim 1 enjoys priority from P4.

23. Art. 54(2) EPC

The Opponents had no objections under Art. 54(2) EPC.
None of the documents on file discloses probes as defined in claim 1 or vectors comprising such probes according to claim 2. The requirements of this article are therefore met.

24. Art. 56 EPC

24.1 The Opponents submitted in essence that the technical problem to be solved was the finding of further mutations of diagnostic value in BRCA1. Its solution was obvious after the publication of D1 and U14680, i.e. after localisation and sequencing of the BRCA1 gene. This reasoning was supported by D91 (a submission by the P in a parallel case) stating that within a matter of weeks after the publication at least two other groups had identified various predisposing mutations. The selection of the 185delAG mutation was arbitrary because there was neither a prejudice nor a particular problem to be overcome nor an unexpected result. The 185delAG mutation was the most common and would thus inevitably have been found in the ongoing screens. Families BOV3 (D9) and 2979 (D42) were both later found to contain this particular mutation (D47).

24.2 Claim 1 is now directed to a nucleic acid probe of specified length and sequence which is suitable to detect a particular mutation in the BRCA1 gene. According to Table 15 and the paragraph bridging pp. 60/61 of the application as filed, the 185delAG mutation is relatively frequent. It was also found multiple times in targeted screening of probands from families with minimal or no family history.

All parties and the OD consider D1 to represent the closest prior art. D1 discloses the gene sequence of BRCA1, lists some predisposing mutations (Table 2) and concludes by stating: Nevertheless, the percentage of total breast and ovarian cancer caused by mutant BRCA1 alleles will soon be estimated, and individual mutations and penetration frequencies may be established. This in turn may predict accurate genetic screening for predisposition to a common deadly disease.

Vis-à-vis D1, the technical problem to be solved is thus the provision of a means to detect a frequently occurring predisposing mutation in BRCA1.

This problem is solved by the probes of claim 1.

The OD agrees with the Os that the mere identification of further predisposing mutations did not pose particular technical problems to the person of skill after the publication of D1. Also, the person of skill certainly had an interest in finding further predisposing mutations (cf. e.g. D9, D12, D42). The Os argued that finding the mutation was a matter of time and since it was a frequent mutation, it would have been found inevitably.
This does however not imply that the person of skill had a reasonable expectation of success of finding a particularly frequent mutation. D1 itself does not provide any information to lead the person of skill to the claimed probes. Also, D1 provides no information about the frequency of individual mutations. Although some publications on file such as D9 or D42 disclose pedigrees of affected families they do not disclose any of the specific mutations because at that time no sequence information was available. For the same reason they cannot provide any information about the frequency of occurrence of particular mutations. Even if one assumes that samples of the affected different families were available to the person of skill, e.g. from D9, D20, or D42 he would not have known which sample to choose from. Therefore, when using D1 alone or in combination with any of the documents D9, D20 or D42, he would not have identified with a reasonable expectation of success the 185delAG mutation as a frequent mutation.
The OD agrees with P's view that the screening for frequently occurring mutations provides an advantage in screening because by screening for the more frequent mutations first, the number of tests and hence the costs may be reduced. This advantage is seen in the application as filed where it is stated that the 185delAG mutation was found multiple times in patients not selected for family history (p.60, line 58 to p. 61, line 2). Therefore, the OD considers the claims of Auxiliary request 3 to involve an inventive step.

25. Art. 52(2) EPC

25.1 O6 cited D89 and submitted in essence that the isolation of the BRCA1 gene or of any human gene for that matter was a mere discovery which constituted no patentable invention.

25.2 European Directive 98/44 EU and the corresponding implementing Regulations of the EPC clearly state that "an element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element" (Rule 23e(2) EPC, Art. 5(2) EU Directive).
The very wording of this implementing Rule contradicts O6's submission. There is no fundamental bar to the patenting of complete or partial human gene sequences (cf. also T272/95, Reasons 4-9).

Claims 1 to 3 directly or indirectly relate to DNAs encoding parts of the human BRCA1 protein, which is described throughout the patent in suit as having been obtained by technical processes (e.g. Example 8). They, thus, meet the definition of patentable elements of the human body given in Rule 23(e)(2) EPC.
Accordingly, they do not fall within the category of inventions which may not be patented for being discoveries (Article 52(2)(a) EPC).

26. Art. 57 EPC

26.1 No objections have been raised against the granted claims to probes or vectors and host cells comprising these probes (granted claims 3 to 6).
The OD notes that the patent application taught the use of probes in diagnosing a predisposition to breast or ovarian cancer (p. 19) and therefore meets the requirement of Rule 23e(3) EPC and Art. 57 EPC.

27. Art. 53(a) EPC

27.1 O6 submitted that the patent should be revoked under Art. 53(a) EPC in view of the socio economic consequences which in this case were well documented (D55-D58, D63, D67). He requested that in analogy with R. 23d(d) EPC there should be found a balance between the benefits and the drawbacks to society due to the grant of a monopoly.

27.2 First, the OD notes that the present set of claims relates to specific probes, vectors and cells, and not to genes. The OD cannot recognize in what respect the publication or exploitation of the now claimed invention, i.e. the defined probes and vectors which are widely considered to be useful in the field of

diagnostics (D108), could be contrary to order public or morality.

Even if the claims were directed to genes, the OD could not follow O6' arguments. As can be taken from the clear wording of Art. 53(a) EPC and from the relevant case law of the EPO boards of appeal (T 19/90, OJ 1990, 476 and T 356/93, OJ 1995, 545; T 272/95 of 23 October 2002), Art. 53(a) EPC can only apply in rather exceptional cases, namely where the publication or exploitation of the invention as claimed is in conflict with basic legal or ethical values. None of the objections raised by O6 is of such nature. O6 focused on possible negative effects of the patenting of the invention in suit and pointed to financial and economic drawbacks or dependencies and negative consequences for the health system. The EPO has however not been vested with the task of taking into account the socio-economic effects of the grant of patents in specific areas and of restricting the field of patentable subject-matter accordingly (G1/98, OJ EPO 2000, 111, Reasons, point 3.9; Guidelines for examination in the EPO, C-IV, 3.3a). The standard to apply for an exclusion under Art. 53(a) EPC is whether the publication or the exploitation of the invention is contrary to ordre public or morality. Art. 53(a) EPC does thus not provide the EPO with the competence to refuse or revoke a patent by assessing certain alleged negative consequences which may result from the grant of an exclusive right in an individual case.

Finally, Rule 23(e)(2) EPC, which corresponds to Art. 5(2) of Directive 98/44 of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions clearly defines which biological material originating from the human body may be patented (cf. pt. 25.2 above). It follows from the text of the Rule itself that the matter of the patent in suit is not to be considered as an exception to patentability under Article 53(a) EPC (see T 272/95 of 23 October 2002, Reasons, 6-9). This is in conformity with the established practice of the EPO (cf. Guidelines, C-IV, 2a.2; see also Relaxin decision, OJ EPO 1995, 388)

28. The OD is therefore of the opinion that the claims of the Auxiliary Request meet the requirements of the EPC.

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Opposition against EP-Patent 0 705 903
(95 30 5605.8)
University of Utah Research Foundation
~~Our Ref.: K2709 OPP(EP) S3~~

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