# EXHIBIT E

EP 95 30 5605.8
Myriad Genetics, Inc.
Our Ref.: K2709 OPP(EP) S3

# MAIN REQUEST

1. 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.

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 a mutation in the sequence of the BRCA1 gene in a sample from said lesion compared to the nucleotide sequence set forth in SEQ ID NO: 1 or a wild-type allelic variant thereof, said mutation being 185delAG→ter39.

3. A method as claimed in claim 1 or 2, which comprises analyzing mRNA of said sample to determine whether an expression product is present indicative of expression of a mutant BRCA1 allele, wherein said mRNA from said sample is contacted with an oligonucleotide BRCA1 gene probe, being allele-specific for said alteration/mutation, under conditions suitable for hybridization of said probe to an RNA corresponding to said BRCA1 gene and hybridization of said probe is determined.

4. A method as claimed in claim 1 or claim 2 wherein an oligonucleotide BRCA1 gene probe, being allele-specific for said alteration/mutation, is contacted with genomic DNA isolated from said sample under conditions suitable for hybridization of said probe to said gene and hybridization of said probe is determined.

5. A method as claimed in claim 1 or claim 2 wherein oligonucleotide primers are employed which are specific for the mutant BRCA1 allele as defined in claim 1 to determine whether said allele is present in said sample by nucleic acid amplification.

6. A nucleic acid probe having 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG→ter39.

7. A replicative cloning vector which comprises an isolated nucleic acid according to claim 6 and a replicon operative in a host cell for said vector.

8. Host cells in vitro transformed with a vector as claimed in claim 7.

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# AUXILIARY REQUEST I

1. A method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is ~~a~~ germline alteration **185delAG→ter39** 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.~~ **GenBank, accession number U-14680 of October 8, 1994**

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 ~~a~~ mutation **185delAG→ter39** in the sequence of the BRCA1 gene in a sample from said lesion compared to the nucleotide sequence set forth in ~~SEQ ID NO: 1 or a wild-type allelic variant thereof, said mutation being 185delAG→ter39.~~ **GenBank, accession number U-14680 of October 8, 1994.**

3. A method as claimed in claim 1 or 2, which comprises analyzing mRNA of said sample to determine whether an expression product is present indicative of expression of a mutant BRCA1 allele, wherein said mRNA from said sample is contacted with an oligonucleotide BRCA1 gene probe, being allele-specific for said alteration/mutation, under conditions suitable for hybridization of said probe to an RNA corresponding to said BRCA1 gene and hybridization of said probe is determined.

4. A method as claimed in claim 1 or claim 2 wherein an oligonucleotide BRCA1 gene probe, being allele-specific for said alteration/mutation, is contacted with genomic DNA isolated from said sample under conditions suitable for

hybridization of said probe to said gene and hybridization of said probe is determined.

5. A method as claimed in claim 1 or claim 2 wherein oligonucleotide primers are employed which are specific for the mutant BRCA1 allele as defined in claim 1 to determine whether said allele is present in said sample by nucleic acid amplification.

6. A nucleic acid probe having 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG→ter39.

7. A replicative cloning vector which comprises an isolated nucleic acid according to claim 6 and a replicon operative in a host cell for said vector.

8. Host cells in vitro transformed with a vector as claimed in claim 7.

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# AUXILIARY REQUEST 2

1. 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 a tissue sample of said subject, said germline alteration indicating a predisposition to said cancer being that, compared to a human BRCA1 gene that has the coding sequence for a full-length human BRCA1 polypeptide, the third nucleotide of codon 22, A, and the first nucleotide of codon 23, G, are deleted resulting in a nucleotide sequence encoding 38 amino acids,
wherein said full-length human BRCA1 polypeptide
   - has 1863 amino acids,
   - has a molecular weight of 208 kilodaltons, and
   - comprises the amino acid sequence of SEQ ID NO: 82,

said coding sequence being comprised in a genomic DNA which is obtainable by:

(a) providing a human genomic library;

(b) screening the genomic library using a probe selected from the group consisting of:

(i) the following DNA sequence:

TGT CCC ATC TGT CTG GAG TTG ATC AAG GAA CCT GTC
TCC ACA AAG TGT GAC CAC ATA TTT TGC AAA TTT TGC
ATG CTG AAA CTT CTC AAC CAG AAG AAA GGG CCT TCA
CAG TGT CCT TTA TGT AAG

(ii) the following DNA sequence:

AG GAA AGT TCT GCT GTT TTT AGC AAA AGC GTC CAG
AAA GGA GAG CTT AGC AGG AGT CCT AGC CCT TTC ACC

CAT ACA CAT TTG GCT CAG GGT TAC CGA AGA GGG GCC
AAG AAA TTA GAG TCC TCA GAA GAG AAC TTA TCT AGT
GAG GAT GAA GAG CTT CCC TGC TTC CAA CAC TTG TTA
TTT GGT AAA GTA AAC AAT ATA CCT TCT CAG TCT ACT
AGG CAT AGC ACC GTT GCT ACC GAG TGT CTG TCT AAG
AAC ACA GAG GAG AAT TTA TTA TCA TTG AAG AAT AGC
TTA AAT GAC TGC A

and

(iii) the DNA sequence of any one of SEQ ID NOs: 35, 38, 41, 42, 47, 57, 62, 67, 72 and 81

and

(c) producing a genomic DNA comprising said coding sequence;

wherein said genomic DNA comprising said coding sequence is more than 100 kb in length; and

wherein the first exon within said genomic DNA immediately follows the nucleotide sequence corresponding to SEQ ID NO: 35; or

said coding sequence being comprised in a cDNA which is obtainable by:

(aa) providing a cDNA library using human mRNA from breast, thymus, testis or ovary;

(bb) screening the cDNA library using a probe selected from the group consisting of:

(i) the following DNA sequence:

TGT CCC ATC TGT CTG GAG TTG ATC AAG GAA CCT GTC
TCC ACA AAG TGT GAC CAC ATA TTT TGC AAA TTT TGC
ATG CTG AAA CTT CTC AAC CAG AAG AAA GGG CCT TCA
CAG TGT CCT TTA TGT AAG

and

(ii) the following DNA sequence:

AG GAA AGT TCT GCT GTT TTT AGC AAA AGC GTC CAG

AAA GGA GAG CTT AGC AGG AGT CCT AGC CCT TTC ACC
CAT ACA CAT TTG GCT CAG GGT TAC CGA AGA GGG GCC
AAG AAA TTA GAG TCC TCA GAA GAG AAC TTA TCT AGT
GAG GAT GAA GAG CTT CCC TGC TTC CAA CAC TTG TTA
TTT GGT AAA GTA AAC AAT ATA CCT TCT CAG TCT ACT
AGG CAT AGC ACC GTT GCT ACC GAG TGT CTG TCT AAG
AAC ACA GAG GAG AAT TTA TTA TCA TTG AAG AAT AGC
TTA AAT GAC TGC A

and

(cc) producing a cDNA comprising said coding sequence;

wherein said coding sequence comprises the following nucleotide sequence:

AG GAA AGT TCT GCT GTT TTT AGC AAA AGC GTC CAG
AAA GGA GAG CTT AGC AGG AGT CCT AGC CCT TTC ACC
CAT ACA CAT TTG GCT CAG GGT TAC CGA AGA GGG GCC
AAG AAA TTA GAG TCC TCA GAA GAG AAC TTA TCT AGT
GAG GAT GAA GAG CTT CCC TGC TTC CAA CAC TTG TTA
TTT GGT AAA GTA AAC AAT ATA CCT TCT CAG TCT ACT
AGG CAT AGC ACC GTT GCT ACC GAG TGT CTG TCT AAG
AAC ACA GAG GAG AAT TTA TTA TCA TTG AAG AAT AGC
TTA AAT GAC TGC A

and

wherein upon hybridization of a Northern blot with a fragment of said cDNA a single transcript of 7.8 kb is identified in breast, thymus, testis and ovary tissue.

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 a mutation in a sample from said lesion, said mutation being that, compared to a human BRCA1 gene that has the coding sequence for a full-length human BRCA1 polypeptide, the third nucleotide of codon 22, A, and the first nucleotide of codon 23, G, are deleted resulting in a

nucleotide sequence encoding 38 amino acids, wherein said full-length human BRCA1 polypeptide and said coding sequence are as defined in claim 1.

3. A method as claimed in claim 1 or claim 2 which comprises analyzing mRNA or protein of said sample to determine whether an expression product is present indicative of expression of a mutant BRCA1 allele.

4. A method as claimed in claim 3 wherein the mRNA encoded by the BRCA1 gene in said sample is investigated.

5. A method as claimed in claim 4 wherein mRNA from said sample is contacted with an oligonucleotide BRCA1 gene probe under conditions suitable for hybridization of said probe to an RNA corresponding to said BRCA1 gene and hybridization of said probe is determined.

6. A method as claimed in claim 1 or claim 2 wherein an oligonucleotide BRCA1 gene probe is contacted with genomic DNA isolated from said sample under conditions suitable for hybridization of said probe to said gene and hybridization of said probe is determined.

7. A method as claimed in claim 5 or 6 wherein said probe is an allele-specific probe for a mutant BRCA1 allele as defined in claim 1.

8. A method as claimed in claim 1 or claim 2 which comprises determining whether there is a mutation in the BRCA1 gene in said sample by observing shifts in electrophoretic mobility of single-stranded DNA from said sample on non-denaturing polyacrylamide gels.

9. A method as claimed in claim 1 or claim 2 wherein all or part of the BRCA1 gene in said sample is amplified and the sequence of said amplified sequence is determined.

10. A method as claimed in claim 1 or claim 2 wherein oligonucleotide primers are

employed which are specific for a mutant BRCA1 allele as defined in claim 1 to determine whether said allele is present in said sample by nucleic acid amplification.

11. A method as claimed in claim 1 or claim 2 wherein all or part of the BRCA1 gene in said sample is cloned to produce a cloned sequence and the sequence of said cloned sequence is determined.

12. A method as claimed in any one of claims 1 to 4 which comprises determining whether there is a mismatch between molecules (1) BRCA1 gene genomic DNA or BRCA1 mRNA isolated from said sample, and (2) a nucleic acid probe complementary to human wild-type BRCA1 gene DNA, when molecules (1) and (2) are hybridized to each other to form a duplex.

13. A method as claimed in any one of claims 1 to 4 wherein amplification of BRCA1 gene sequences in said sample is carried out and hybridization of the amplified sequences to one or more nucleic acid probes which comprise a wild-type BRCA1 gene sequence or a mutant BRCA1 gene sequence as defined in claim 1 is determined.

14. A method as claimed in claim 1 or claim 2 which comprises determining in situ hybridization of the BRCA1 gene in said sample with one or more nucleic acid probes which comprise a wild-type BRCA1 gene sequence or a mutant BRCA1 gene sequence as defined in claim 1.

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

16. A replicative cloning vector which comprises an isolated nucleic acid according to claims 15 and a replicon operative in a host cell for said vector.

17. Host cells in vitro transformed with a vector as claimed in claim 16.

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## AUXILIARY REQUEST III

1. A nucleic acid probe ~~having~~ consisting of 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG→ter39.

2. 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.

3. Host cells in vitro transformed with a vector as claimed in claim 2.

D108

# An External Quality Assessment scheme for genetic testing of familial Breast / Ovarian Cancer

Clemens R. Mueller[1], Dominique Stoppa-Lyonnet[2], Ulf Kristoffersson[3]

[1] University of Wuerzburg, Wuerzburg, Germany, [2] Institut Curie, Paris, France, [3] Lund University Hospital, Lund, Sweden

## INTRODUCTION

Breast and ovarian cancers (Br/Ov) are the most frequent cancers in women with a life-time risk of about 10 % in Western countries. About 5 % of all cases are thought to be familial due to mutations in the BRCA1 and BRCA2 genes. Given the prevalence of Br/Ov cancers, mutation screening of the BRCA genes is now being offered to at risk women. The main benefit of mutation detection is the predictive testing of relatives of identified mutation carriers. In 1999 a pilot External Quality Assessment (EQA) scheme was offered by the **European Molecular Genetics Quality Network (EMQN)** for the genetic testing of the BRCA1 gene. Following the successful trial, the scope of the scheme was widened in 2000 to include a case of a predictive test for a known family mutation and testing for the BRCA2 gene. The scheme was also offered to a wider audience of laboratories. The breakdown of participants by country is given in **Table 1.**

**Table 1: EQA scheme participants**

| Country | 1999 | 2000 |
|---|---|---|
| Australia | - | 1 |
| Belgium | 3 | 5 |
| Czech Republic | 1 | 1 |
| Cyprus | - | 1 |
| Denmark | 1 | 1 |
| France | 9 | 5 |
| Germany | 2 | 1 |
| Israel | 1 | - |
| Italy | - | 3 |
| Latvia | - | 1 |
| Sweden | 2 | 1 |
| The Netherlands | 1 | 4 |
| United Kingdom | 1 | 3 |
| Total | 21 | 28 |
| No results returned | 7 | 3 |

## CASES AND QUESTIONS

In 1999, three genomic DNA samples were distributed and the analysis of exons 2, 13 and 17 of the BRCA1 gene was requested (**Table 2**). In 2000 the scheme included two samples for the BRCA1 gene (exons 2 and 11) plus one sample for BRCA2, exon 27 (**Table 3**). In both years, missense ("unclassified variants") and truncating mutations had to be detected, the 2000 scheme included a predictive diagnosis for the prevalent Ashkenazi mutation in the BRCA1 gene, 185delAG. This way, the most common situations for interpretation were covered. Various mutation (pre-)screening methods were used but results were based on sequence data in all but one cases.

**Table 2: 1999 cases**

| Gene | Exon | Nt change | AA change | Conclusions |
|---|---|---|---|---|
| BRCA1 | 2 | C140T | Arg7 > Arg | UV, splice site activation? Risk unchanged |
| BRCA1 | 17 | A5176G | His1686 > Arg | UV, causal role possible but not proven, risk unchanged |
| BRCA1 | 13 | C4446T | Arg1443 > Stop | Truncating mutation, highly probable to be causal, life-time risk increased |

**Table 3: 2000 cases**

| Gene | Exon | Nt change | AA change | Conclusions |
|---|---|---|---|---|
| BRCA1 | 2 | 185delAG | frameshift | carrier, high life-time risk |
| BRCA1 | 11 | 1259delG | frameshift | truncating, highly probable to be causal, life-time risk increased |
| BRCA2 | 27 | A10462G | Ile3412 > Val | UV, polymorphism, risk unchanged |

## MATERIALS

Thanks to generous gifts of the Curie Institute in Paris, all samples could be prepared from cell lines. No problems with the quality of the samples were reported, a few labs asked for a second sample for confirmation which was provided

## RESULTS

The overall results are listed in **Table 4** based on the total number of reports returned and the total number of cases analysed.

**Table 4: EQA scheme results**

| Year | 1999 | 2000 |
|---|---|---|
| Samples sent out | 21 | 28 |
| Reports returned | 14 | 25 |
| Cases analysed | 40 | 68 |
| Diagnostic errors (mistakes leading to wrong diagnosis) | 1 | 4 |
| Error rate (diagnostic error/cases analysed) | 2.5% | 5.8% |
| Genotyping marks (Mean: max. of 2.00 points) | 1.83 | 1.76 |
| Interpretation marks (Mean: max of 2.00 points) | 1.61 | 1.46 |

As was observed in other schemes, the error rate went up and the average marks decreased with the opening of the scheme to a broader participation. Most likely, this reflects the real situation better than the initial pilot scheme for which "the" national experts are likely to be nominated.

In the 1999 scheme, the sequence change C140T in exon 2 of BRCA1 (case 1) was not detected in 1 laboratory. One lab refused to analyse a sample because it was from a non-affected woman. Another lab found an extra sequence change in one sample. Both cases caused subsequent discussions (see below).

In the 2000 scheme, the sequence change 1259delG in exon 11 of BRCA1 (case 2) was not detected by 2 laboratories. The sequence change A10462G in exon 27 of BRCA2 (case 3) was not detected by 2 other labs.

## ADMINISTRATION AND ASSESSMENT

Some participants were hard to contact by e-mail because of hand-written addresses. Online subscription may be a better option in the future. Reports were accepted either as hard copies or e-mail attachments. One e-mail did not at all reach the scheme provider. A brief confirmation of receipt of the scheme materials (by the participants) and of the reports (by the scheme provider) may help to identify mailing problems early on.

Dominique Stoppa-Lyonnet (Paris) and Ulf Kristofferson (Lund) served as assessors. During the evaluation of the reports it was very helpful to have the expertise of a molecular biologist (DSL) and a clinical geneticists (UK).

## PARTICIPANTS FEEDBACK

There were only a few comments by the participants, mainly dealing with problems of marking or nomenclature. The refusal by one lab to test an unaffected woman was based on a misunderstanding of the scheme's intentions. Schemes are not designed to catch out participants or to test laboratory policies. A difficult case arose when one lab found two mutations in one sample, including the "true" one. Their report was not clear on the interpretation of this unusual result and initially scored as a diagnostic error. Upon the participant's complaint, the assessors' scoring was revised after consultation with the EMQN office.

## CONCLUSIONS

The experiences from this scheme illustrate the well known problems associated with the use of DNA sequencing to identify unknown heterozygous mutations. Although sequencing is regarded as the "gold standard" of mutation detection by many, it requires careful internal and external quality assessment to arrive at the desired high sensitivity and specificity.

## ADDITIONAL INFORMATION

### REFERENCES

European Best Practice Guidelines for familial Breast/Ovarian Cancer
www.emqn.org/bpguidelines

### THE SCHEME

THE FAMILIAL BREAST/OVARIAN CANCER SCHEME IS ORGANISED AND RUN BY THE EUROPEAN MOLECULAR GENETICS QUALITY NETWORK (EMQN)

Contact Dr Simon Patton or Dr Rob Elles, Regional Molecular Genetics laboratory, St Mary's Hospital, Hathersage Road, Manchester M13 0JH, UK. Tel: +44.161.276.6741/6129. Email: office@emqn.org

EMQN is funded by the European Commission (Contract No. SMT4-CT98-7515)

### RELATED POSTERS

P1077- The European Molecular Genetics Quality Network
P1079 - EQA scheme for Huntington Disease
P1080 - EQA scheme for Duchenne Muscular Dystrophy
P1081 - EQA scheme for Friedreich Ataxia
P1082 - EQA scheme for Charcot Marie Tooth Disease
P1083 - EQA scheme for Y-Chromosome Microdeletions

Europäisches Patentamt
GD2-Einspruch

European Patent Office
DG2 - Opposition

Office européen des brevets
DG2 - Opposition

Application No.: 95 305 605.8

Patent No.: EP-B-0705903

# Minutes of the oral proceedings before the OPPOSITION DIVISION

The proceedings were public.

**Proceedings opened** on 24.01.2005 at 0905 hours

**Present as members of the opposition division:**

| | |
|---|---|
| Chairman: | Isert, B |
| 1st member: | Stolz, B |
| 2nd member: | Sprinks, M |
| Legal member: | Treichel, P |
| Minute writer: | Sprinks, M |

**Present as or for the party or parties:**

- For the Proprietor(s): THE UNIVERSITY OF UTAH RESEARCH FOUNDATION

  H.R. Jaenichen (Representative)
  O. Malek (European Patent Attorney)
  D. Shattuck (Inventor)

- For the Opponent 1: INSTITUT CURIE

  J. Warcoin (Representative)
  F. Faivre Petit (European Patent Attorney)
  D. Stoppa-Lyonnet (Technical Expert)
  F. Lazard
  D. Delaplace

- For the Opponent 2: ASSISTANCE PUBLIQUE-HOPITAUX DE PARIS

  c.f. O1

- For the Opponent 3: INSTITUT GUSTAVE ROUSSY-IGR

  c.f. O1

- For the Opponent 4: Vereniging van Stichtingen Klinische Genetica

  W. Bird (Representative)
  I. De Baere (Candidate)
  L. Paemen
  G. Matthijs (Technical Expert)

- For the Opponent 5: De Staat der Nederlanden
  Minister van Volksgezondheid, Welzijn en Sport

  B. Swinkels (Representative)

## Documents for the maintenance of the patent as amended

**Auxiliary Request 3**

In the text for the Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

**Description, Pages**

| | |
|---|---|
| 25-59, 61-138 | of the patent specification |
| 3-24, 60 | filed during Oral proceedings on 25.01.2005 |

**Claims, Numbers**

| | |
|---|---|
| 1-3 | filed during Oral proceedings on 24.01.2005 |

**Drawings, Figures**

| | |
|---|---|
| 1-10 | of the patent specification |

- For the Opponent 6: Greenpeace e.V.

  C. Then (Representative)

The identity of the person/s (as well as, if applicable, that of the witness or witnesses) and, where necessary, the authorisation to represent/authority to act were checked.

Essentials of the discussion and possible relevant statements of the parties:

After deliberation of the opposition division,

- the chairman announced the following **decision**:

**"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 European Patent Convention. The currently valid documents are those according to the claims of Auxiliary Request III filed on 24.01.05; amended pages 3-24 and 60 of the description filed on 25.01.05; pages 1-2, 25-59 and 61-138 of the description and figures 1-10H of the patent as granted.."**

Regarding the reasons for the decision, the chairman referred to:

Article 102(3) EPC.

The party/parties was/were informed that the minutes of the oral proceedings and a written reasoned decision (including an indication of the possibility of appeal) will be notified to him/them as soon as possible.

The chairman **closed the oral proceedings** on 25.01.2005 at 1405 hours.

Isert, B
Chairman

Sprinks, M
Minute Writer

Annex(es):
Main and Aux. Requests I-III, description p.3-24 and 60, D108

Form 2339.4

1. The chairman of the Opposition Division (OD) opened the proceedings at 0905 on 24.01.05 and briefly reviewed the file. He informed the parties that the proceedings would be sound recorded in accordance with the **Guidelines E-III, 10.1**.

2. The Proprietor (P) stated that he maintained his main request (MR) and auxiliary requests (AR) filed on 23.11.04 and asked for the opportunity to draft new ARs.

3. All six opponents (O) requested complete revocation. In addition O5 requested either that no further amendments to the requests be allowed, giving procedural abuse as the reason, or if further requests were allowed, that proceedings be suspended and costs be apportioned.

4. The chairman opened discussion on the MR w.r.t. **Article 123(2)(3) and 84 EPC**. O1-3 objected to claim 1 under **Art. 123(2) EPC**, reasoning that there was no original disclosure of a wild type allelic variant as a reference sequence. O1-3 added that there was only one mutation selected and this specific selection was not supported and that for claims 6-8, the range of 15-30 was not supported and that no specific length of probe was disclosed. Under **Art. 84 EPC** O1-3 stated that the expression wild type variant was unclear, particularly in a screening method. O4 agreed with O1-3 and added that claim 1 added matter by mosaicing features. O5 added that the arbitrary selection of a particular mutation in claim 1 added matter as it was targeted at Ashkenazi Jews and that this connection was only disclosed after filing. Furthermore, the size of 30 in claim 6 was only originally disclosed for a specific method and mutations. O6 added nothing.

5. P stated that the expression "wild type allelic variant" could not be objected to now as it was in the granted claims and the application as filed and had not changed. P added that the particular mutation in claim 1 was already in the list of mutations in granted claim 16 and could not legally be considered unclear. All that had been done was to delete all unpatentable mutations. P gave Example 15, Tables 14-17 and the paragraph bridging page 60 and 61 of the published application as basis for the mutation, and cited T10/97 to support the allow ability of deleting individual members from a list. W.r.t. the basis for the range of 15-30 nucleotides in claim 6, P indicated granted claim 3 as basis together with page 10 lines 29-34, page 11 line 12 and the section entitled "probes" starting on page 14 line 55. P also cited

T201/83 and T925/98, adding that there could be no **Art. 123(3)** objection as this was a restriction.

6. O1-3 reiterated that there was no original disclosure of using a wild type sequence as a reference for comparison and O4 repeated that this was unclear. OD asked P why he had chosen the range 15-30. P replied that it was so that the claim didn't include anything that had changed in the priority. After a short break, P indicated that page 15 line 8 was additional basis for this range selection.

7. After deliberation, the chairman gave the OD's opinion that the MR fulfilled the requirements of **Art. 123(2)(3) and 84 EPC** and opened the discussion on **Art. 83 EPC**.

8. O1-3 stated that the term wild type was not defined and therefore could not be used to make a comparison for pathology. O4 agreed and O5 added that one couldn't differentiate between non-predisposing alterations and mutants. P replied that those in the art could carry out the claim and that the opponents had done it. P requested that D108 be admitted in support of this and added that it should be attempted to make technical sense of the claim, citing T552/00 and T190/99, and that with only one mutation this was easy.

9. OD requested a copy of D108. After taking time to study the document, the chairman asked the parties for their comments. O1-3 requested that this document not be admitted as it was filed too late. O4 and O5 stated that it was not relevant to the use of wild type alleles and O4 added that it showed that in 5.8% of cases there were problems with errors. P referred to D104 in support that the method could be carried out, adding that there are false positives and negatives in any screening method. O4 submitted that Dr. Becker (D104) took risks with the analysis.

10. OD decided to admit D108 as relevant and after deliberation, the chairman gave the OD's opinion that the MR fulfilled the requirements of **Art. 83 EPC**. The chairman then opened the discussion on **Art. 87 EPC**.

11. O1-3 maintained that only the fifth priority (P5) was valid as claim 1 referred to SEQ ID NO:1 and that this was different in the fourth priority (P4). O1-3 added

that the mutation 185delAG-ter39 indicated the position of an AG in the sequence and that in P4 position 185 corresponded to AC instead - therefore the P4 sequence could not be used as a reference. O4-6 agreed.

P replied that the mutation name indicated a termination codon and that if one tried to make technical sense of the claim it would be clear where the mutation should be. P referred to Exhibit 1A, and Example 15 and page 95 line 7 of P4.

O4 referred to G2/98 and stated that the Enlarged Board of Appeal interpreted the principal of same invention narrowly. Subject-matter had to be the same for priority to be valid. This was extremely important for **Art. 54(3)**. O4 referred to T0351/01 in which differences outside the coding region were still considered to result in different subject-matter. O4 stated that SEQ ID NO:1 was an essential feature of claim 1, also because, absent any functional assay, it was needed to define the wild type allelic variants referred to therein. O5 agreed and added that priority was not the same as inventive step - no experiments to correct mistakes were allowed.

P again referred to Example 15 and stated that the technical contribution should be considered. One would only look at the relevant place in the gene to find the mutation and this had not been changed.

O4 stated that the sequence information was essential for the method of diagnosis as one had to be certain that any mutation was linked to disease. O5 quoted P as saying that formal requirements should be balanced with the technical contribution. O5 said that P4 was after the Science publication (D4) and that P chose to have SEQ ID NO:1 in the claims. P replied that 15 irrelevant changes wouldn't change the diagnosis. After breaking for lunch, P added that on page 95, P4 showed that 68 people were tested and diagnosed showing that the sequence changes didn't make a difference.

12. After deliberation, the chairman gave the OD's opinion that the first valid priority for the MR was P5. He then opened the discussion on novelty.

13. O1-3 referred to D5 and D6, particularly Table 3, stating that both described the mutation in claim 1 in the context of the claimed screening method. O4-6 and PR had nothing to add.

14. After a break, the chairman gave the OD's opinion that claims 1 and 2 of the MR were not novel over at least D5.

15. P asked to submit a new AR I (see Annex). He stated that P4 referred to Genbank entry U14680 and that D107 showed its history. He indicated the reference to U14680 in the application as filed on page 43 line 6, and on page 43 of the granted patent, stating that the screening method using U14680 hadn't changed since P4.

16. OD asked P why this request was filed so late. P replied that it had only come to mind after the oral proceedings on a related case the week before, during which an AR with product-by-process claims had not been allowed.

17. O5 strongly objected to the admission of the new request, stating that it had caught the opponents off guard. It raised so many issues with **Art. 123(2)(3), 84 and 87 EPC** that he requested suspension of the proceedings if it was admitted. PR replied that the opponents had already known of U14680 as prior art and that the claim was simple to understand. O1-3 said that to go from the product-by-process claims of original AR I to new claims referring to U14680 was a complete change of claim form and raised issues with **Art. 123(2)(3) EPC**. O4 asked OD to consider **Rule 71a(2) EPC** as P had been aware of the problems with SEQ ID NO:1 and consequently the new claims were filed too late.

18. After a break for cogitation, the chairman informed the parties that in the interests of procedural fairness, the new AR could not be accepted by OD as the problems with SEQ ID NO:1 had been known for some time. The request was therefore denied in accordance with **Rule 71a(2) and Article 114(2) EPC**. Pr then requested renumbering of the ARs such that the new AR became AR I, AR I became AR II etc.

19. The chairman opened discussion on AR II w.r.t. **Art. 123(2)(3) and 84 EPC**.

20. O1-3 stated that the product-by-process claims were not acceptable under **Art. 123(2) EPC** as there was no basis in the original application for combining a process of isolating coding sequences and then restricting the results using the parameters of length and molecular weight. Furthermore, the claim required a combination of elements from 13 different passages in the application and that parts b(i) and bb(i) required the use of a sequence as a probe, which use was not in P4 or the application as filed. W.r.t. **Art. 123(3) EPC**, O1-3 said that the claims also encompassed the use of pathological genes in the method, broadening the scope of protection. W.r.t. **Art 84 EPC**, O1-3 stated that the expression "being comprised" in claim 1 was of indefinite scope, that there was no indication of how the molecular weight was to be measured, that the term "wherein" suggested only a result to be achieved, and that claim 1 was not concise as it covered 3 pages, such that its scope was impossible to determine without undue burden.

21. O4 stated that the human BRCA1 sequence now referred to was different to that of the granted claim and that it was P's responsibility to prove that there was no extension of scope under **Art 123(3) EPC**. W.r.t. **Art 123(2) EPC**, O4 said that claim 1 was a mosaic of features not linked in the application as originally filed and that there was no basis for "producing a genomic DNA". O4 also objected to the claim for lack of clarity as the form was so complex, and for lack of support as no genomic DNA was produced in the description. Under **Art 123(3) EPC**, O5 added that the parameters of 1863 amino acids and the molecular weight of 208 kilodaltons were only originally disclosed in the context of SEQ ID NO:2. O5 added that in the sense of T0552/91, product-by-process claims should only be used in exceptional circumstances and the result should be specific, and that this was not the case here.

22. P cited T552/91 and T923/92 adding nothing more.

23. After a break for consideration, the chairman gave the OD's decision that AR II was not acceptable under **Art. 123(2)(3) or 84 EPC**. Discussion began on AR III w.r.t **Art. 123(2)(3), 84 and 87 EPC**

24. O1-3 stated that SEQ ID NO:1 was still in claim 1 and therefore P5 was still to be considered the first valid priority. O4 considered "having" to mean "comprising" such that the claim encompassed the whole of SEQ ID NO:1. P replied that the

structural formula had never change since P4 and that therefore P4 was valid.

25. In order to clarify the situation, OD asked P directly if the wording "having" encompassed nucleic acids longer than 30 nucleotides. P replied that the probe could not be "extraordinarily long". After O1-3 and O4 reiterated their arguments, P clearly stated that the claims covered probes longer than 30 nucleotides but added that it would make no technical sense to make them longer than 1308 nucleotides. O4 replied that the application described probes from 15 to 6000 nucleotides and that since no use was specified in the claim, the whole of SEQ ID NO:1 was covered.

26. After deliberation, OD announced that it still considered P5 not P4 as the first valid priority since "having" was clearly intended to be interpreted in an open-ended manner in the claim and therefore covered sequence that had changed between them.

27. P then submitted a new AR and abandoned previous AR III. The new AR became AR III (see Annex), in which the expression "having" was replaced with "consisting of". The chairman then announced a break until the following day.

28. The chairman summarised the proceedings of the previous day and opened discussion on the new AR III.

29. P stated that the request had been made to overcome the priority problem. None of the opponents had any objections w.r.t. admissibility, **Art. 123(2)(3), 83 or 84 EPC**.

30. O1-5 maintained that P5 was still the first valid priority. O6 agreed. P stated that the opponents had not indicated why they thought it was not the same invention as P4, since the part of SEQ ID NO:1 referred to in the claim had not changed.

31. After a brief pause for OD to confer, the chairman gave the OD's opinion that P4 was valid for AR III and opened discussion on **Art. 54 EPC**. None of the opponents had objections under novelty. Consequently, the chairman announced that the subject-matter of the claims was novel and opened discussion on **Art 56 EPC**.

32. O1-3 stated that if P4 was considered valid then D1 and D4 were the most relevant documents and the problem to be solved was to find new mutations in BRCA1. He added that P had created a new problem by limiting the invention to the specific population of Ashkenazi Jews and that this was not in the patent application. O1-3 said that access to a particular population did not make an inventive step and that the problem was not relevant, citing D29 and D45 as the first time it was mentioned. He also said that this was an ex post facto analysis, cited T268/89, adding that in D41 two populations were checked and that just because the mutation was found more in one than the other it didn't justify an inventive step.

O4 wanted it on record that he was not motivated by any political party. He agreed with O1-3's formulation of the technical problem and expressed concerns about the claims in connection with **Art. 52(4) EPC**. He cited T0024/91 and G5/85 and defined the skilled person as a team of scientists comprising a doctor who had a civic duty and access to normal patient information and DNA samples. O4 cited D6 page 397 to show that the methodology was standard and that screening could be done on "whichever patient comes through the door". He also cited D1 Table 2 on page 69, pointing to the kindred 1901 mutation 188del11 as an indication that a skilled person would look in exon 2 for further mutations and find that of the invention. O4 added that D9 disclosed family BOV3 which in D47 was later found to contain the mutation in the claims and added D42 and D20 as further support that samples were freely available which would have made it extremely easy to find the mutation.

O5 added that the kindred 1901 mutation was "right next door" to the mutation in the claims and that post-published D3 showed that certain primers would have provided the appropriate fragment.

O6 stated that finding a new structure alone did not make an invention but that a new function was required.

P replied that a surprising technical effect could be used to support inventive step and that the claimed mutation was surprisingly common, as disclosed in the patent. He stressed that one could always use an effect found later in for inventive step. P pointed out that the connection to Ashkenazi Jews was not important for

inventive step, but simply that the mutation was highly relevant. He pointed out that no diagnostic process was claimed. P said that this mutation was not an arbitrary selection because it was particularly relevant similar to particularly useful mutants. P cited T737/96 and stated that a hope to succeed was not enough. He added that the high mutation rate at this particular position made the claimed mutation particularly useful for a screening process and that its unexpected existence and properties made it inventive in a similar way to inventive splice variants, citing T182/03.

O1-3 insisted that high frequency of a mutation was not an inventive effect but simply made it easy to find. O4 added that it was not like the case with a new chemical compound with unexpected properties, but rather the result of obvious analysis, continuing that the mutation in D5 Table 3 (188del) had the same technical effect. O5 stated that the analogy to T737/96 was not relevant and O6 stated that to do business was not a technical problem.

P said that a skilled person needed a reason to try and a reasonable expectation of success, and that as far as obviousness was concerned, an organised search was irrelevant if the result was surprising. OD asked P if he considered the fact that the mutation was common to be the technical effect. P replied that it was hindsight that it was common. OD asked P about the availability of familial DNA in D9 (BOV3)and D42 (2979). P replied that the families were not identified so one could not get probes. O1-5 reiterated their previous arguments. P replied that the fact that D1 looked at lots of families and did not show the mutation meant that it was not inevitable.

33. After a break for cogitation, the chairman announced that the OD found the subject-matter of AR III to be inventive. He then opened discussion on **Art. 52, 53 and 57 EPC**.

34. O1-5 did not speak. O6 said that it was impossible to examine the ethical relevance and external effects of patent monopolisation, citing G1/98. He added that patents shouldn't damage society and that monopoly of patient DNA was unethical, especially when some patients did not agree, when the disease had a life-threatening character and when one patient group was affected.

P replied that no-one expected the EPO to grant unethical patents. He added that any doctor could visit Myriad's homepage and order a test, and that without monopoly there would be fewer diagnostics.

O6 said that the patent was concerned with getting money back for time and that this was not to do with patent law. He also expressed concerns about the separation of testing and counselling. OD asked O6 which of his submissions were relevant to the claims of AR III. O6 cited D67.

P pointed out that the EPO had developed principals for biotechnology according to the EU Biotechnology Directive, adding that just because one person had said that certain genes shouldn't be patented it didn't correspond to patent law. O6 pointed out that the list of exceptions to patentability in **Rule 23d EPC** was not exhaustive.

35. After a further break for discussion, the chairman announced that the OD found the subject-matter of AR III to comply with **Art. 52, 53 and 57 EPC**. He asked the parties if they had any further requests. O5 mentioned his earlier request that no further requests of P be admitted. The chairman indicated that OD had already rendered this moot by refusing to admit AR I with its Genbank reference. No party had any further requests.

36. P was asked to file an amended description which he did. After O1-6 made requests for and agreed further amendments, the chairman announced OD's decision to maintain the patent in amended form based on AR III filed during the proceedings on 24.01.05 and pages of the description filed on 25.01.05.

37. Oral proceedings were closed at 1405 on 25.01.05.

Annex

EP 95 30 5605.8
Myriad Genetics, Inc.
Our Ref.: K2709 OPP(EP) S3

## MAIN REQUEST

1. 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.

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 a mutation in the sequence of the BRCA1 gene in a sample from said lesion compared to the nucleotide sequence set forth in SEQ ID NO: 1 or a wild-type allelic variant thereof, said mutation being 185delAG→ter39.

3. A method as claimed in claim 1 or 2, which comprises analyzing mRNA of said sample to determine whether an expression product is present indicative of expression of a mutant BRCA1 allele, wherein said mRNA from said sample is contacted with an oligonucleotide BRCA1 gene probe, being allele-specific for said alteration/mutation, under conditions suitable for hybridization of said probe to an RNA corresponding to said BRCA1 gene and hybridization of said probe is determined.

4. A method as claimed in claim 1 or claim 2 wherein an oligonucleotide BRCA1 gene probe, being allele-specific for said alteration/mutation, is contacted with genomic DNA isolated from said sample under conditions suitable for hybridization of said probe to said gene and hybridization of said probe is determined.

5. A method as claimed in claim 1 or claim 2 wherein oligonucleotide primers are employed which are specific for the mutant BRCA1 allele as defined in claim 1 to determine whether said allele is present in said sample by nucleic acid amplification.

6. A nucleic acid probe having 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG→ter39.

7. A replicative cloning vector which comprises an isolated nucleic acid according to claim 6 and a replicon operative in a host cell for said vector.

8. Host cells in vitro transformed with a vector as claimed in claim 7.

24/1/05

EP 95 30 5605.8
Myriad Genetics, Inc.
Our Ref.: K2709 OPP(EP) S3

# AUXILIARY REQUEST I

1. A method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is ~~a~~ germline alteration **185delAG→ter39** 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.~~ **GenBank, accession number U-14680 of October 8, 1994.**

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 ~~a~~ mutation **185delAG→ter39** in the sequence of the BRCA1 gene in a sample from said lesion compared to the nucleotide sequence set forth in ~~SEQ ID NO: 1 or a wild-type allelic variant thereof, said mutation being 185delAG→ter39.~~ **GenBank, accession number U-14680 of October 8, 1994.**

3. A method as claimed in claim 1 or 2, which comprises analyzing mRNA of said sample to determine whether an expression product is present indicative of expression of a mutant BRCA1 allele, wherein said mRNA from said sample is contacted with an oligonucleotide BRCA1 gene probe, being allele-specific for said alteration/mutation, under conditions suitable for hybridization of said probe to an RNA corresponding to said BRCA1 gene and hybridization of said probe is determined.

4. A method as claimed in claim 1 or claim 2 wherein an oligonucleotide BRCA1 gene probe, being allele-specific for said alteration/mutation, is contacted with genomic DNA isolated from said sample under conditions suitable for

hybridization of said probe to said gene and hybridization of said probe is determined.

5. A method as claimed in claim 1 or claim 2 wherein oligonucleotide primers are employed which are specific for the mutant BRCA1 allele as defined in claim 1 to determine whether said allele is present in said sample by nucleic acid amplification.

6. A nucleic acid probe having 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG→ter39.

7. A replicative cloning vector which comprises an isolated nucleic acid according to claim 6 and a replicon operative in a host cell for said vector.

8. Host cells in vitro transformed with a vector as claimed in claim 7.