EXHIBIT 1
(PART 1 OF 2)

ISSUE CLASSIFICATION	
Class	Subclass
435	6

[redacted]

5709999

5709999

UTILITY SERIAL NUMBER	PATENT DATE	PATENT NUMBER
08/483553	JAN 20 1998	

SERIAL NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
08/483,553	06/07/95	435	6	~~1802~~ 1807	Rees

APPLICANTS: DONNA M. SHATTUCK-EIDENS, SALT LAKE CITY, UT; JACQUES SIMARD, ST-AUGUSTIN DE DESMAURES, CANADA; FRANCINE DUROCHER, STE-FOY, CANADA; MITSUURU EMI, TOKOYO, JAPAN; YUSUKE NAKAMURA, YOKOHAMA-SHI, JAPAN.

CONTINUING DATA*******************
VERIFIED THIS APPLN IS A CIP OF 08/409,305 03/24/95 ABN
WHICH IS A CIP OF 08/348,824 11/29/94 ABN
✓DR 6/2/96 WHICH IS A CIP OF 08/308,104 09/16/94
WHICH IS A CIP OF 08/300,266 09/02/94 ABN
WHICH IS A CIP OF 08/289,221 08/12/94 ABN

FOREIGN/PCT APPLICATIONS**********
VERIFIED

NONE DR 6/2/96

CERTIFICATE
DEC 08 1998
OF CORRECTION

FOREIGN FILING LICENSE GRANTED 12/22/95

Foreign priority claimed / 35 USC 119 conditions met / Verified and Acknowledged		AS FILED	STATE OR COUNTRY	SHEETS DRWGS.	TOTAL CLAIMS	INDEP. CLAIMS	FILING FEE RECEIVED	ATTORNEY'S DOCKET NO.
yes ☐ no ☒ / yes ☐ no ☒	Examiner's initials DR	→	UT	19	16	1	$860.00	24884-109347

ADDRESS:
VENABLE BAETJER HOWARD AND CIVILETTI
1201 NEW YORK AVENUE NW
SUITE 1000
WASHINGTON DC 20005

TITLE: LINKED BREAST AND OVARIAN CANCER SUSCEPTIBILITY GENE

U.S. DEPT. OF COMM./PAT. & TM—PTO-436L (Rev.12-94)

PARTS OF APPLICATION FILED SEPARATELY

Applications Examiner

NOTICE OF ALLOWANCE MAILED		CLAIMS ALLOWED	
April 22, 1997	DIANNE REES Assistant Examiner	Total Claims 35	Print Claim 1

ISSUE FEE			DRAWING		
Amount Due $1290.00	Date Paid 7/14/97	W. GARY JONES SUPERVISORY PATENT EXAMINER GROUP 1800 Primary Examiner	Sheets Drwg. 18	Figs. Drwg. 19	Print Fig. 1

ISSUE BATCH NUMBER Z-99

Label Area

PREPARED FOR ISSUE

WARNING: The information disclosed herein may be restricted. Unauthorized disclosure may be prohibited by the United States Code Title 35, Sections 122, 181 and 368. Possession outside the U.S. Patent & Trademark Office is restricted to authorized employees and contractors only.

Form PTO-436A
(Rev. 8/92)

ISSUE FEE IN FILE

(FACE)

briefed in group 1800

PATENT APPLICATION

08483553

APPROVED FOR LICENSE

INITIALS 9591

08/483553

Date Entered or Counted

CONTENTS

Date Received or Mailed

RECEIVED JAN - 5 1996 GROUP 1800

Date Entered or Counted	No.	Contents	Date Received or Mailed
	1.	Application papers.	
	2.	Pre Decafee	8/14/95
	3.	Res Sequence Listing (OK)	8/23/95
	4.	Exchange Dec	10-26-95
	5.	Ext of time	10-26-95
	6.	IDS	10-12-95
	7.	Prel Amdt A	1-29-96
	8.	Petition	1/29/96
	9.	Decision on Pet	5/16/96
	10.	Rej 3 month	6-18-96
	11.	Supplemental IDS w/Attch	2-23-96
	12.	Amdt B	9-12-96
	12 1/2	Supple Amdt C	11-5-96
	13.	Fin Rej 3 mos	12-3-96
	14.	Amdt D (E)	12-9-96
	15.	F. Rej. 3 ms.	02-05-97
	16.	Interview Summary	2/12/97
	17.	ExMRS Amdt/E	04-22-97
10/20/97	18.	Formal Drawings 26 shts set 1	7/14/97
	19.	PTO Grant JAN 20 1998	
	20.	C of C	5-19-98
	21.	Approved in Part	9-29-98
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6/10 11/25 2/3 4/18

(FRONT)

BAR CODE LABEL

U.S. PATENT APPLICATION

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT
08/483,553	06/07/95	435	1802

APPLICANT

DONNA M. SHATTUCK-EIDENS, SALT LAKE CITY, UT; JACQUES SIMARD, ST AUGUSTIN DE, CANADA; FRANCINE DUROCHER, STE-FOY, CANADA; MITSUURU EMI, TOKOYO, JAPAN; YUSUKE NAKAMURA, YOKOHAMA-SHI, JAPAN.

CONTINUING DATA********
VERIFIED

THIS APPLN IS A CIP OF 08/409,305 03/24/95
WHICH IS A CIP OF 08/348,824 11/29/94
WHICH IS A CIP OF 08/308,104 09/16/94
WHICH IS A CIP OF 08/300,266 09/02/94 ABN
WHICH IS A CIP OF 08/289,221 08/12/94

FOREIGN/PCT APPLICATIONS********
VERIFIED

FOREIGN FILING LICENSE GRANTED 12/22/95

STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS	FILING FEE RECEIVED	ATTORNEY DOCKET NO.
UT	19	16	1	$860.00	24884-109347

ADDRESS

VENABLE BAETJER HOWARD AND CIVILETTI
1201 NEW YORK AVENUE NW
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WASHINGTON DC 20005

TITLE

LINKED BREAST AND OVARIAN CANCER SUSCEPTIBILITY GENE

This is to certify that annexed hereto is a true copy from the records of the United States Patent and Trademark Office of the application which is identified above.

By authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

Date Certifying Officer

Notice of Allowability	Application No. 08/483,553	Applicant(s) Shattuck-Eidens et al.
	Examiner Dianne Rees	Group Art Unit 1807

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course.

☒ This communication is responsive to *telephone interview of 2/12/97*.

☒ The allowed claim(s) is/are *1-5,7-11,13-15,17-20,22-25,27-30,32-40,42,43 renumbered as 1-36*.

☐ The drawings filed on _____ are acceptable.

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE **THREE MONTHS** FROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

☒ Applicant MUST submit NEW FORMAL DRAWINGS

☒ because the originally filed drawings were declared by applicant to be informal.

☐ including changes required by the Notice of Draftsperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. _____.

☐ including changes required by the proposed drawing correction filed on _____, which has been approved by the examiner.

☐ including changes required by the attached Examiner's Amendment/Comment.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal lettter addressed to the Official Draftsperson.

☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Interview Summary, PTO-413

☒ Examiner's Amendment/Comment

☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material

☒ Examiner's Statement of Reasons for Allowance

DETAILED ACTION

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Jeffrey Inhen on February 12, 1997.

2. The application has been amended as follows:

In claim 1, after "said human sample", the words --with the proviso that said germline alteration is not a deletion of 4 nucleotides corresponding to base numbers 4184-4187 of SEQ ID NO: 1-- have been added.

In claim 13, after "14" the words --with the proviso that said germline alteration is not a deletion of 4 nuclectides corresponding to base numbers 4184-4187 of SEQ ID NO: 1-- have been added.

In claim 15, after "14" the words --with the proviso that said germline alteration is not a deletion of 4 nucleotides corresponding to base numbers 4184-4187 of SEQ ID NO: 1-- have been added.

Claims 21,26 ,31, 36, 41 have been canceled.

In claim 19, line 1, "is" has been deleted and --consists of-- has been inserted.

In claims 23,28,33,38, and 43 the words "the alteration comprising" have been deleted.

In claims 22,24,27,29,32,34,37,39, and 42, the words, "comprising the alteration comprising" has been deleted, and --consists of-- inserted.

3. The following is an examiner's statement of reasons for allowance:

The claims are drawn to methods of detecting germline alterations in the BRCA1 gene by detecting alterations in BRCA1 nucleic acids. In a further embodiment of the claims, the method is used to detect specific polymorphisms in the BRCA1 gene. Applicant is first to disclose the mutational analysis of the sequence of the BRCA1 gene and the specific mutations recited herein.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue

fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dianne Rees whose telephone number is (703) 6565.

W. GARY JONES
SUPERVISORY PATENT EXAMINER
GROUP 1800
4/18/97

Dianne Rees
April 15, 1997

[redacted]

5710001

5710001

Class	Subclass	ISSUE CLASSIFICATION
435	6	093

UTILITY SERIAL NUMBER	PATENT DATE	PATENT NUMBER
08/487,002	JAN 20 1998	5710001

SERIAL NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
08/487,002	06/07/95	435	6	1805	Doc

APPLICANTS

MARK H. SKOLNICK, SALT LAKE CITY, UT; DAVID E. GOLDGAR, SALT LAKE CITY, UT; YOSHIO MIKI, SALT LAKE CITY, UT; JEFF SWENSON, SALT LAKE CITY, UT; ALEXANDER KAMB, SALT LAKE CITY, UT; KEITH D. HARSHMAN, SALT LAKE CITY, UT; DONNA M. SHATTUCK-EIDENS, SALT LAKE CITY, UT; SEAN V. TAVTIGIAN, SALT LAKE CITY, UT; ROGER W. WISEMAN, DURHAM, NC; P. ANDREW FUTREAL, DURHAM, NC.

CONTINUING DATA********
VERIFIED
THIS APPLN IS A CIP OF 08/409,305 03/24/95 ABN
WHICH IS A CIP OF 08/348,824 11/29/94 ABN
WHICH IS A CIP OF 08/308,104 09/16/94 ABN
WHICH IS A CIP OF 08/300,266 09/02/94 ABN
WHICH IS A CIP OF 08/289,221 08/12/94 ABN

DR 5/29/96

FOREIGN/PCT APPLICATIONS********
VERIFIED

NONE DR 5/29/96

NOTE-DISCLAIMER
The term of this patent shall not extend beyond the expiration date of Pat. No.

FOREIGN FILING LICENSE GRANTED 02/28/96

Foreign priority claimed 35 USC 119 conditions met	Verified and Acknowledged	Examiner's initials	AS FILED	STATE OR COUNTRY	SHEETS DRWGS.	TOTAL CLAIMS	INDEP. CLAIMS	FILING FEE RECEIVED	ATTORNEY'S DOCKET NO.
☐ yes ☒ no ☐ yes ☐ no		DR	→	UT	19	28	2	$1,056.00	24884-109347

ADDRESS
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1201 NEW YORK AVENUE NW
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TITLE
170-LINKED BREAST AND OVARIAN CANCER SUSCEPTIBILITY GENE

U.S. DEPT. OF COMM./ PAT. & TM—PTO-436L (Rev.12-94)

PARTS OF APPLICATION FILED SEPARATELY

Application Examiner

NOTICE OF ALLOWANCE MAILED
8-18-97

DIANNE REES
Assistant Examiner

CLAIMS ALLOWED

Total Claims	Print Claim
35	1

ISSUE FEE

Amount Due	Date Paid
$1290.00	

W. GARY JONES
SUPERVISORY PATENT EXAMINER
GROUP 1800
Primary Examiner

DRAWING

Sheets Drwg.	Figs. Drwg.	Print Fig.
18	19	0

PREPARED FOR ISSUE

ISSUE BATCH NUMBER 299

WARNING: The information disclosed herein may be restricted. Unauthorized disclosure may be prohibited by the United States Code Title 35, Sections 122, 181 and 368. Possession outside the U.S. Patent & Trademark Office is restricted to authorized employees and contractors only.

FORM PTO-1267 (Rev. 11-92) U.S. Department of Commerce Patent and Trademark Office

DISCLAIMER LABEL

Application No. 08/487,002

A terminal disclaimer has been entered and recorded under 35 U.S.C. 253 in this file.

DO NOT DESTROY

Form PTO-436A (Rev. 8/92)

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(FACE)

briefed in group 1800

08/ 08/487002

PATENT APPLICATION

08487002

APPROVED FOR LICENSE

INITIALS JUL 2 0 95 25

CONTENTS

Date Entered or Counted		Contents	Date Received or Mailed
	1.	Application papers.	RECEIVED MAR 27 1996 GROUP 1800
	2.	Statement 1.8?	6/7/95
	3.	Raw Sequ. Listing (CRF)	8/3/95
	4.	Sequ. Fee	8-11-95
	4½ 5.	Sequ. Disclosure / Dec + Fee	12-14-95 / 12-4-95
	6.	Supplemental Disclosure	2-23-96
	7.	Prel. Amdt A	3-15-96
	8.	Petition to Make Special	3-15-96
	9.	Decision on Pet	5/8/96
	10.	Req 3 mos	6-12-96
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	12.	Amdt B	9-12-96
	13.	Supl amdt C	9-17-96
	14.	T.D.	9-12-96
	15.	Supple Amdt D	10-7-96
	16.	Supple Amdt E	11-7-96
	17.	Declaration	11-7-96
	18.	Supple Amdt F	1-14-97
	19.	F/R 3 mos	02-05-97
	20.	Amdt G (NE)	2/25/97
Dey	21.	Interview Summary	4/18/97
	22.	Supple Amdt / H	5-13-97
	23.	Petition / Drawings	7-14-97
	24.	Letter	9-29-97
	25.	PTO Grant JAN 2 0 1998	
	26.	Assoc P/A + Change of Address	1-5-98
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(FRONT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re. Application of:

Mark H. SKOLNICK et al.

Serial No. 08/487,002 Group Art Unit: 1807

Filed: 07 June 1995 Examiner: D. Rees

For: 17q-LINKED BREAST AND OVARIAN CANCER SUSCEPTIBILITY GENE

AMENDMENT

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

In response to the Office Action mailed 12 June 1996, please amend the above-identified application as follows:

IN THE SPECIFICATION

On page 1, line 7, after "1995," please insert -- now abandoned, --.

On page 1, line 7, after "1994," please insert -- now abandoned, --.

On page 1, line 8, after "1994," please insert -- now abandoned, --.

On page 1, line 9, after "1994," please insert -- now abandoned, --.

On page 1, line 10, after "1994," please insert -- now abandoned, --.

IN THE CLAIMS

Please cancel claims 5, 9, 15, 20-24 and 26-28.

Please amend the claims as follows:

360 TL 22-0261 10/07/96 08487002
36027 148 110.00CH

-- Claim 1 (amended). A method for screening [diagnosing] a [lesion] tumor sample from a human subject for a somatic alteration in [neoplasia at the] a BRCA1 gene in said tumor [a human subject] which comprises [detecting an alteration in the sequence of the BRCA1 gene or its expression products in said subject by] comparing [the] a first sequence selected ~~from~~ the group consisting of [the] a BRCA1 gene from said tumor sample, [or] BRCA1 RNA [its expression products in] from said tumor [a] sample [from a lesion of said subject] and BRCA1 cDNA made from mRNA from said tumor sample with a second [the] sequence selected from the group consisting of [the wild-type] BRCA1 gene from a nontumor sample of said subject, BRCA1 RNA from said nontumor sample [or] and BRCA1 cDNA made from mRNA from said nontumor sample, [its expression products] wherein [an alteration] a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said tumor sample from the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said nontumor sample [subject] indicates [neoplasia at] a somatic alteration in the BRCA1 gene in said tumor sample. --

-- Claim 3 (amended). The method of claim 1 wherein [said expression product is mRNA of the BRCA1 gene] a nucleic acid sequence of BRCA1 RNA from the tumor sample is compared to nucleic acid sequences of wild-type BRCA1 gene, BRCA1 RNA or BRCA1 cDNA. --

-- Claim 4 (amended). The method of claim 3 wherein the [alteration of the mRNA is detected] nucleic acid sequence is compared by hybridizing [hybridization of the mRNA of said sample with] a BRCA1 gene probe specific for a BRCA1 allele to RNA isolated from said tumor sample and detecting the presence of a hybridization product, wherein a presence of said product indicates the presence of said allele in the tumor sample. --

-- Claim 6 (amended). The method of claim 1 wherein [an alteration is detected in the] a regulatory [regions] region of the BRCA1 gene from said subject is compared with a regulatory region of wild-type BRCA1 gene sequences, said regulatory region corresponding to nucleotides 1-1531 of SEQ ID NO:13. --

-- Claim 7 (amended). The method of claim 1 wherein the [alteration in the germline] nucleic acid sequence is [detected] compared by forming single-stranded DNA from a BRCA1

gene fragment from said sample and from a corresponding fragment of a wild-type BRCA1 gene, electrophoresing said single-stranded DNAs on a non-denaturing polyacrylamide gel, comparing the [observing shifts in electrophoretic] mobility of said single-stranded [DNA] DNAs on [non-denaturing polyacrylamide gels] said gel to determine if said single-stranded DNA from said sample is shifted relative to wild-type and sequencing said single-stranded DNA having a shift in mobility. --

-- Claim 8 (amended). The method of claim 1 wherein the [alteration of the germline] nucleic acid sequence is [detected] compared by hybridizing [hybridization of] a BRCA1 gene probe specific for a BRCA1 allele to genomic DNA isolated from said [tissue] sample and detecting the presence of a hybridization product, wherein the presence of said product indicates the presence of said allele in the tumor sample. --

-- Claim 10 (amended). The method of claim 1 wherein the [alteration in the germline] nucleic acid sequence is [detected] compared by amplifying all or part of the BRCA1 gene from said sample using a set of primers to produce [an] amplified nucleic acids [sequence] and sequencing the amplified nucleic acids [sequence]. --

-- Claim 11 (amended). The method of claim 1 wherein the [alteration in the germline] nucleic acid sequence is [detected] compared by amplifying [all or] part of the BRCA1 gene using a primer specific for a specific BRCA1 [mutant] altered allele and detecting the presence of an amplified product, wherein the presence of said product indicates the presence of said specific allele. --

-- Claim 12 (amended). The method of claim 1 wherein the [alteration in the germline] nucleic acid sequence is [detected] compared by molecularly cloning all or part of the BRCA1 gene from said sample to produce a cloned nucleic acid [sequence] and sequencing the nucleic acid cloned sequence. --

-- Claim 13 (amended). The method of claim 1 wherein an [the alteration in the germline] nucleic acid sequence is [detected] compared by forming a heteroduplex consisting of

a first strand of nucleic acid selected from the group consisting of [identifying a mismatch between molecules (1)] BRCA1 gene genomic DNA fragment isolated from said sample, BRCA1 RNA fragment isolated from said sample [or] and BRCA1 cDNA fragment made from mRNA [isolated] from said sample and a second strand of [(2)] a nucleic acid consisting of [probe complementary to the] a corresponding human wild-type BRCA1 gene fragment, [DNA when molecules (1) and (2 are hybridized to each other to form a duplex] analyzing for the presence of a mismatch in said heteroduplex and sequencing said first strand of nucleic acid having a mismatch. --

-- Claim 14 (amended). The method of claim 1 wherein the [alteration in the germline] nucleic acid sequence is [detected] compared by amplifying [amplification of] BRCA1 gene sequences [in] from said sample to produce amplified nucleic acids, hybridizing [and hybridization of] the amplified [sequences] nucleic acids to [nucleic acid probes which comprise wild-type BRCA1 gene sequences] a BRCA1 DNA probe specific for a BRCA1 allele and detecting the presence of a hybridization product, wherein a presence of said product indicates the presence of said allele in the sample. --

-- Claim 16 (amended). The method of claim 1 wherein the [alteration in the germline] nucleic acid sequence is [detected] compared by [screening] analyzing BRCA1 gene sequences in said sample for a deletion mutation. --

-- Claim 17 (amended). The method of claim 1 wherein the [alteration in the germline] nucleic acid sequence is [detected] compared by [screening] analyzing BRCA1 gene sequences in said sample for a point mutation. --

-- Claim 18 (amended). The method of claim 1 wherein the [alteration in the germline] nucleic acid sequence is [detected] compared by [screening] analyzing BRCA1 gene sequences in said sample for an insertion mutation. --

-- Claim 19 (amended). The method of claim 1 wherein the [alteration in the germline] nucleic acid sequence is [detected] compared by hybridizing a tumor *in situ* [hybridization of the

BRCA1 gene] with a nucleic acid [probes which comprise the BRCA1 gene] probe specific for a BRCA1 allele and detecting the presence of a hybridization product, wherein the presence of said product indicates the presence of said allele in said tumor. --

Please add the following new claims:

--29. The method of claim 1 wherein a nucleic acid sequence of BRCA1 cDNA made from mRNA from the tumor sample is compared to nucleic acid sequences of wild-type BRCA1 gene, BRCA1 RNA or BRCA1 cDNA. --

-- 30. The method of claim 1 wherein a nucleic acid sequence of BRCA1 gene from the tumor sample is compared to nucleic acid sequences of wild-type BRCA1 gene, BRCA1 RNA or BRCA1 cDNA. --

-- 31. A method for detecting an alteration in a BRCA1 gene from a tumor sample from a human subject, said alteration consisting of the alterations set forth in Tables 11 and 12, which comprises analyzing a sequence of a BRCA1 gene or BRCA1 RNA from a sample of said tumor or analyzing the sequence of BRCA1 cDNA made from mRNA from said sample. --

-- 32. The method of claim 31 wherein an alteration is detected by hybridizing a BRCA1 gene probe specific for an allele of one of said alterations to RNA isolated from said sample and detecting the presence of a hybridization product, wherein the presence of said product indicates the presence of said allele in the tumor. --

-- 33. The method of claim 31 wherein an alteration is detected by hybridizing a BRCA1 gene probe specific for an allele of one of said alterations to genomic DNA isolated from said sample and detecting of the presence of a hybridization product, wherein the presence of said product indicates the presence of said alteration in the tumor. --

22-34. The method of claim 31 wherein an alteration is detected by amplifying all or part of a BRCA1 gene in said sample using a set of primers to produce amplified nucleic acids and sequencing the amplified nucleic acids. --

-- 35. The method of claim 31 wherein an alteration is detected by amplifying part of a BRCA1 gene in said sample using a primer specific for an allele having one of said alterations and detecting the presence of an amplified product, wherein the presence of said product indicates the presence of said allele in the tumor. --

-- 36. The method of claim 31 wherein an alteration is detected by molecularly cloning all or part of a BRCA1 gene in said sample to produce a cloned nucleic acid and sequencing the cloned nucleic acid. --

-- 37. The method of claim 32 wherein an alteration is detected by amplifying BRCA1 gene nucleic acids in said sample, hybridizing the amplified nucleic acids to a BRCA1 DNA probe specific for one of said alterations and detecting the presence of a hybridization product, wherein the presence of said product indicates the presence of said alteration. –

-- 38. A method for screening a tumor sample from a human subject for the presence of a somatic alteration in a BRCA1 gene in said tumor which comprises comparing BRCA1 polypeptide from said tumor sample from said subject to BRCA1 polypeptide from a nontumor sample from said subject to analyze for a difference between the polypeptides, wherein said comparing is performed by (i) analyzing for a truncated protein in each sample or (ii) binding an antibody specific to an epitope of an altered BRCA1 polypeptide to the BRCA1 polypeptide from each sample and detecting antibody binding, wherein a difference between the BRCA1 polypeptide from said tumor sample from BRCA1 polypeptide from said nontumor sample indicates the presence of a somatic alteration in the BRCA1 gene in said tumor sample. --

-- 39. The method of claim 38 wherein a BRCA1 polypeptide is analyzed by detecting a truncated BRCA1 polypeptide. --

-- 40. The method of claim 38 wherein a BRCA1 polypeptide is analyzed by binding an antibody specific to an epitope of an altered BRCA1 polypeptide to the BRCA1 polypeptide from said sample and detecting antibody binding. --

REMARKS

The undersigned wishes to thank the Examiner for the courtesies extended to Dr. Mark Skolnick and himself during the interview on 10 September 1996 directed to the present application as well as several related applications.

The specification has been amended to indicate the current status of the parent applications. In accordance with the Examiner's suggestion, the claims have been amended to be directed to a method for screening a tumor sample for a somatic alteration in a BRCA1 gene. The claims have further been amended to set forth each of the process steps as set forth in the specification and known in the art.

Claim 1 has further been amended so that it is directed to nucleic acid analysis. Claim 6 has been amended to specify a regulatory region of a BRCA1 gene to correspond to a sequence shown in SEQ ID NO:13. Support for this amendment can be found at page 77, lines 7-22. New claims 29 and 30 have been added to claim the material tested, similar to claim 3. New claims 31-37 have been added to claim a method for detecting in a tumor the specific alterations set forth in Table 11 and 12. New claims 38-40 have been added to claim the analysis of a BRCA1 polypeptide to screen for the somatic alterations, and find their support in claims 5, 20 and 21 as originally filed. The analysis is specifically directed to detecting a truncated protein by binding an antibody specific to an epitope of an altered BRCA1 polypeptide. It is believed that none of these amendments constitute new matter.

It is believed that the above amendments obviate the 35 USC §112, second paragraph rejection of the claims. Withdrawal of this rejection is requested.

Similarly, it is believed that the above amendments obviate the 35 USC §112, first paragraph rejection of the claims. The general nature of this rejection and claim amendments were discussed during the interview as noted on the interview summary record. Dr. Skolnick and the Examiner each noted the recognized utility for alterations in the BRCA1 gene which lead to deleterious effects in the protein. Dr. Skolnick also discussed the utility for other alterations including polymorphisms. He noted that the three types of alterations are (a) those

that are neutral, (b) those that are causal and (c) those that are not clear. Each of these types of alterations are useful for making a judgment concerning the risk of developing cancer from the involvement of the BRCA1 gene. Dr. Skolnick indicated that any risk assessment has utility and any alteration provides screening data which is used in assessing or weighing the risk of developing cancer. He noted, for example, that a person may have an alteration for which the effect is not clear. However, this person would know that she did not have a wild-type gene and therefore, on average, would have a higher risk than someone with no alteration. A sister of this person who did not have the alteration would then know that she has a normal risk from this factor. In addition, Dr. Skolnick noted that each type of alteration is useful in the analysis of ethnic background and penetrance of the BRCA1 gene in different populations. He also noted that although a BRCA1 gene heterozygosity may exist in the germline, a homozygosity in expression has been seen. Thus, it is possible to screen for a lack of a transcript. He indicated that heterozygosity in germline to homozygosity in expression may occur about 10-15% of the time.

Dr. Skolnick noted that a detection of an alteration in the germline is an indication of predisposition to cancer and a detection of a somatic alteration in a tumor is an indication of progression towards neoplasia. He indicated that a somatic mutation, including loss of all or part of the BRCA1 gene, is generally seen in the chromosome opposite the chromosome with a germline alteration in the BRCA1 gene, ans is also rarely seen in ovarian tumors.

Dr Skolnick also briefly discussed how the BRCA1 gene is currently analyzed for alterations. He indicated that 35 primers are currently used to amplify the DNA and then this DNA is sequenced. Generally one pair of primers is used per exon and surrounding intron. Since exon 11 is large, it is broken up into several overlapping primer pairs. The BRCA1 gene is amplified with each primer pair. The resulting amplified DNA is the sequenced in both the forward and reverse directions. Dr. Skolnick indicated that they are currently processing 25 BRCA1 patient samples per day. The technique of using a set of primers allows for the amplification of all or part of the BRCA1 gene as now set forth in claims 10 and 34.

The enablement of the screening for alterations in the BRCA1 gene using a polypeptide was also briefly discussed. Dr. Skolnick noted that the molecular weight of the BRCA1 polypeptide is known and is around 220 kilodaltons. He also noted that antibodies to BRCA1 polypeptide are commercially available from a number of labs. The Examiner noted that the

detection of a truncated protein was enabled. She also noted that the skill in the art for the development of antibodies to proteins was really high. The nature of antibodies to detect an alteration was discussed. New claims 38 and 40 which are directed to binding an antibody to a BRCA1 polypeptide contains the limitation that the antibody is specific for an epitope of an altered BRCA1 polypeptide. Thus, the antibody recognizes and binds to a BRCA1 polypeptide with an altered sequence. It is well known in the art that the epitope must be accessible to the antibody in order for it to bind. In view of the high skill in the art for making antibodies against proteins and determining epitopes to which they bind, it is submitted that it is not undue experimentation to prepare an antibody which would be specific for an altered BRCA1 polypeptide. To further demonstrate these facts, Applicants are in the process of preparing an appropriate declaration and will submit it as soon as it is completed.

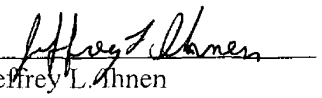
In view of the amendments to the claims and the above remarks, it is believed that the claims are enabled in accordance with 35 USC §112, first paragraph. Withdrawal of this rejection is requested.

The claims were rejected for obviousness-type double patenting over Serial Nos. 08/409,305 and 08/483,553. Serial No. 08/409,305 was expressly abandoned on 10 September 1996. The present claims are directed to methods for detecting somatic alterations in the BRCA1 gene or specific somatic alterations set forth in Tables 11 or 12. The claims of Serial No. 08/483,553 are directed to methods for detecting specific germline mutations set forth in Tables 12A, 14, 18 or 19. The Tables of 08/483,553 do not contain any of the alterations set forth in Tables 11 or 12 of the present application. There is no disclosure in the present application which would make the specific alterations of Serial No. 08/483,553 obvious or would suggest such specific alterations to a skilled artisan. Consequently, it is submitted that the claims of the present application are patentably distinct over the claims of Serial No. 08/483,553. Withdrawal of these rejections is requested.

Applicants note that the claims of related application Serial No. 08/488,011 were rejected for obviousness-type double patenting over the claims of the present application. In view of this rejection in the related application, Applicants are submitting a Terminal Disclaimer with this Amendment. In addition, Applicants direct the attention of the Examiner to a further related application Serial No. 08/483,554 which contains claims to wild-type BRCA1, mutant BRCA1 and a method of identifying mutant BRCA1.

In view of the above amendments and remarks, it is believed that the claims satisfy the provisions of 35 USC §112 and are in condition for allowance. Since it is believed that all of the issues raised in the Office Action have been overcome, the Examiner is invited to telephone the undersigned to resolve any further issues and to expedite the prosecution of this application. Reconsideration of this application and early notice of allowance is requested.

Respectfully submitted,



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