Prevalence of *BRCA1* and *BRCA2* Mutations Among Patients With Ovarian, Primary Peritoneal, and Fallopian Tube Cancer in India: A Multicenter Cross-Sectional Study

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**PURPOSE** There are deficient data on prevalence of germline mutations in breast cancer susceptibility genes 1 and 2 (*BRCA1*/*BRCA2*) in Indian patients with ovarian cancer who are not selected by clinical features.

**METHODS** This prospective, cross-sectional, noninterventional study in nine Indian centers included patients with newly diagnosed or relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer. The primary objective was to assess the prevalence of *BRCA1/BRCA2* mutations, and the secondary objective was to correlate *BRCA1/BRCA2* status with clinicopathologic characteristics. Mutation testing was performed by a standard next-generation sequencing assay.

**RESULTS** Between March 2018 and December 2018, 239 patients with a median age of 53.0 (range, 23.0-86.0 years) were included, of whom 203 (84.9%) had newly diagnosed disease, 36 (15.1%) had family history of ovarian or breast cancer, and 159 (66.5%) had serous subtype of epithelial ovarian cancer. Germline pathogenic or likely pathogenic mutations in *BRCA1* and *BRCA2* were detected in 37 (15.5%; 95% CI, 11.1 to 20.7) and 14 (5.9%; 95% CI, 3.2 to 9.6) patients, respectively, whereas variants of uncertain significance in these genes were seen in four (1.7%; 95% CI, 0.5 to 4.2) and six (2.5%; 95% CI, 0.9 to 5.4) patients, respectively. The prevalence of pathogenic or likely pathogenic *BRCA* mutations in patients with serous versus nonserous tumors, with versus without relevant family history, and ≤ 50 years versus > 50 years, were 40 of 159 (25.2%; 95% CI, 18.6 to 32.6) versus 11 of 80 (13.8%; 95% CI, 7.1 to 23.3; *P* = .0636), 20 of 36 (55.6%; 95% CI, 38.1 to 72.1) versus 41 of 203 (20.2%; 95% CI, 14.9 to 26.4; *P* < .0001), and 20 of 90 (22.2%; 95% CI, 14.1 to 32.2) versus 31 of 149 (20.8%; 95% CI, 14.6 to 28.2; *P* = .7956), respectively.

**CONCLUSION** There is a high prevalence of pathogenic or likely pathogenic germline *BRCA* mutations in Indian patients with ovarian cancer.

**INTRODUCTION** Ovarian cancer is one of the most common gynecologic cancers, with 313,959 new cases and 207,252 deaths reported worldwide in 2020. It accounted for more deaths than any other cancer of the female reproductive system. In the Indian context, ovarian cancer is the third leading cancer among women, after cervical and breast cancer.

A majority of patients with ovarian cancer are diagnosed at an advanced stage, wherein the 5-year survival is < 30%. Family history of ovarian or breast cancer is one of the important predisposing factors, with first- and second-degree relatives having four-fold and two-fold higher risk of developing ovarian cancer, respectively. Inherited mutations in the key tumor suppressor genes, the breast cancer susceptibility gene 1 or 2 (*BRCA1* or *BRCA2*), are prevalent in 3%-27% of patients with ovarian cancer who are not selected on the basis of clinical features like family history. By age 70 years, ovarian cancer risk is 40% in *BRCA1* and 18% in *BRCA2* mutation carriers. Germine mutations in *BRCA* genes also confer high risk for the development of fallopian tube carcinoma and primary papillary serous carcinoma of the peritoneum. Some studies have suggested that ovarian cancer patients with germline *BRCA1/2* mutations (especially *BRCA2*) have improved prognosis compared with those lacking *BRCA* mutations.
In this multicenter Indian study involving nine tertiary centers and 239 patients, germline pathogenic or likely pathogenic mutations in BRCA1 and BRCA2 were detected in 15.5% and 5.9% of patients, respectively. The prevalence of these mutations in patients with nonserous tumors, without relevant family history, and with age > 50 years was 13.8%, 20.2%, and 20.8%, respectively. This suggests that selection of patients for germline testing by serous histology, suggestive family history, and young age is likely to miss BRCA1 and BRCA2 mutations in many patients.

Relevance
There is a high incidence of germline BRCA1 and BRCA2 mutations in Indian patients with epithelial ovarian cancer. Efforts should be made to make such testing widely available in India.

by numerous clinical guidelines, screening for BRCA mutations may help not only in developing patient management strategies but also in prognosticating patients with ovarian cancer. For example, the recent National Comprehensive Cancer Network guidelines (version 1, 2020) recommend genetic testing for BRCA1/2 mutations along with other panels of mutations like CDH1, PALB2, PTEN, and TP53 in patients with breast cancer, ovarian cancer, and pancreatic cancer on the basis of their family history, ethnicity, age, and tumor histology. Although a few regional studies have been reported, these have included patients with breast and/or ovarian cancer who were chosen because of clinical features like suggestive family history or young age, with pathogenic or likely pathogenic mutation being reported in 25.5%-30.1% of them. Hence, this multicenter Indian study was undertaken in patients with ovarian cancer not selected for any predisposing clinical features, who were evaluated for prevalence of germline BRCA mutations and its association with clinical and pathologic characteristics.

METHODS
The study protocol (ClinicalTrials.gov identifier: NCT03471572) was approved by the regulatory authorities and the ethics committees or institutional review boards of all the participating centers. The study was conducted in accordance with the Declaration of Helsinki, the International Council on Harmonization Good Clinical Practice guidelines, Good Pharmacoepidemiological Practice, and the applicable legislation(s) on noninterventional studies and/or observational studies. All patients provided written informed consent before their study participation.

Study Population
Women age 18 years or older with previously or newly diagnosed ovarian, primary peritoneal, or fallopian tube cancer were enrolled in the study. Patients were excluded if they failed to provide written informed consent or had any medical condition that, in the opinion of the investigator, would interfere with safe completion of the study, or were participating in any other clinical trial.

Study Design and End Points
This was a prospective, noninterventional, cross-sectional, multicenter study that enrolled patients between March 2018 and December 2018 at 9 centers across India (Appendix Table A1). Data pertaining to demographics, family history of breast and/or ovarian cancer, and medical and surgical history were collected from patients’ available medical records and transcribed on to the electronic case report forms. Blood samples were collected, coded for confidentiality, stored at ambient temperature, and sent to a central laboratory at Bangalore, India, for germline mutation testing. DNA was extracted from blood using a QIAamp DNA mini kit (Qiagen, Germany), and next-generation sequencing (NGS) was performed on the extracted DNA using the TruSight cancer sequencing panel (Illumina, San Diego, CA), covering 94 high-risk genes associated with cancer predisposition. The list of genes is the same as that previously reported. From 50 ng of input genomic DNA of each patient, NGS libraries were prepared and hybridized to a custom pool of oligonucleotides, targeting genomic regions as previously described, followed by paired end sequencing of up to 150 base pair read lengths. The mutations were classified as pathogenic or likely pathogenic or variants of uncertain significance (VUS) as per International Agency for Research on Cancer classification. At the devolution visit, the investigator informed patients about their BRCA mutation test results and appropriate genetic counseling was provided as per the local standard of care. The primary objective was to determine the proportion of patients with germline pathogenic or likely pathogenic BRCA1 and BRCA2 mutations and variants of uncertain significance. We also assessed the association of BRCA1 and BRCA2 mutation with family history of breast and/or ovarian cancer and histopathologic type of ovarian
A majority of patients (230, 96.2%) had ovarian cancer followed by primary peritoneal cancer (8, 3.3%) and fallopian tube cancer (1, 0.4%). Most patients (203, 84.9%) did not have a family history of ovarian or breast cancer.

Prevalence of BRCA1 and BRCA2 Mutations

Of the analyzed 239 patients, pathogenic or likely pathogenic BRCA1/2 mutations were detected in 51 (21.3%; 95% CI, 16.3 to 27.1) patients, 37 (15.5%; 95% CI, 11.1 to 20.7) with BRCA1 mutations and 14 (5.9%; 95% CI, 3.2 to 9.6) with BRCA2 mutations. None of the patients had mutations in both genes. Variants of uncertain significance (VUS) were detected in 10 (4.2%; 95% CI, 2.0 to 7.6) patients, four (1.7%; 95% CI, 0.5 to 4.2) in BRCA1 and six (2.5%; 95% CI, 0.9 to 5.4) in BRCA2. Among the 61 patients with BRCA1/2 or VUS mutations, the numbers of patients (percentage) with frameshift mutation, missense mutation, nonsense mutation, splice site mutation, and other mutations were 31 (50.8%), 13 (21.3%), eight (13.1%), four (6.6%), and five (8.2%), respectively (Fig 1).

Table 2 presents the prevalence and distribution of BRCA mutations according to the number of lines of systemic therapy and family history. Of the 182 (76.2%) patients who had received ≤1 line of treatment, 36 (19.8%; 95% CI, 14.3 to 26.3) had germline pathogenic or likely pathogenic mutation compared with 15 of 57 (26.3%; 95% CI, 18.6 to 32.6) in BRCA1 and six (2.5%; 95% CI, 0.9 to 5.4) in BRCA2. Among the 36 patients with family history of breast and/or ovarian cancer, 20 (55.6%; 95% CI, 38.1 to 72.1) had pathogenic or likely pathogenic BRCA1/2 mutations compared with 41 of 203 (20.2%; 95% CI, 14.9 to 26.4) patients with no family history (P < .0001). There was a trend toward higher prevalence of pathogenic or likely pathogenic BRCA1/2 mutations in patients with serous subtype of ovarian cancer (40 of 159, 25.2%; 95% CI, 18.6 to 32.6) compared with patients with nonserous subtypes (11 of 80, 13.8%; 95% CI, 7.1 to 23.3; Fig 2). Among patients with known endometrioid, clear cell, or mucinous histology, two of 34 (5.9%; 95% CI, 0.7 to 19.7) had germline pathogenic or likely pathogenic BRCA1/2 mutations, including, notably, none of the 15 patients with clear cell or mucinous histology. There was no statistically significant difference in the association of BRCA mutations with tumor histology (P = .0636). There was no significant association of pathogenic or likely pathogenic BRCA1/2 mutations with patients’ age, with prevalence being 20 of 90 (22.2%; 95% CI, 14.1 to 32.2) in patients ≤50 years compared with 31 of 149 (20.8%; 95% CI, 14.6 to 28.2) in patients >50 years (P = .7956; Table 3). The variations for the detected mutations in BRCA 1/2 are reported in Appendix Table A2.

DISCUSSION

Our analysis in this multicenter cohort of Indian patients with ovarian or primary peritoneal cancer suggests a high prevalence (21.3%) of germline pathogenic or likely pathogenic mutations in BRCA1 or BRCA2 genes with an
additional 4.2% having variants of uncertain significance in these genes. To our knowledge, this is the first such report in a cohort from India that is not selected by clinical features like family history and provides important, clinically actionable information of relevance to patients and physicians.

Of note, our analysis suggests that, although the prevalence of \textit{BRCA1/2} mutations was higher in patients with family history of breast and/or ovarian cancer, a considerable minority of patients without such history (20.2%) also harbored the mutations. This suggests that the absence of family history is not adequate as a screening strategy for germline testing. The prevalence of these mutations was higher in patients with serous histology, and no patient with known clear cell or mucinous tumors had a pathogenic mutation, suggesting that histologic subtype may be used to triage patients for testing. Age was not associated with the prevalence of these mutations and should not be incorporated in clinical decision making to test for germline predisposition. The commonest pathogenic mutation reported in this data set was the 187delAG in \textit{BRCA1} (c.68-69delAG in four patients, Appendix Table A2), which is a

![FIG 1. (A) Distribution of pathogenic or likely pathogenic and VUS \textit{BRCA1/2} mutations per mutation type (n = 61). (B) \textit{BRCA1} (n = 41). (C) \textit{BRCA2} (n = 20). VUS, variant of uncertain significance.]

**TABLE 2. Prevalence and Distribution of \textit{BRCA} Mutations**

| Finding                                                                 | No. (%) of Patients (N = 239) |
|------------------------------------------------------------------------|-------------------------------|
| Pathogenic or likely pathogenic \textit{BRCA1/2} germline mutations, No. (%) | 51 (21.3)                     |
| \textit{BRCA1} mutation\(^a\)                                         | 37 (15.5)                     |
| \textit{BRCA2} mutation\(^b\)                                         | 14 (5.9)                      |
| Distribution of \textit{BRCA} mutations as per lines of therapy, No. (%)\(^c\) |                                |
| Pathogenic or likely pathogenic \textit{BRCA1/2} germline mutations receiving \(\leq 1\) line of therapy | 36 of 182 (19.8)             |
| Pathogenic or likely pathogenic \textit{BRCA1/2} germline mutations receiving \(\geq 2\) lines of therapy | 15 of 57 (26.3)              |
| \(P\)                                                                  | .2932                         |

Distribution of \textit{BRCA} mutations as per family history, No. (%)

| Patients with family history of ovarian and/or breast cancer | 36 (15.1) |
| \textit{BRCA} mutations and family history of ovarian and/or breast cancer | 20 (55.6)\(^c\) |
| Patients without family history of ovarian and/or breast cancer | 203 (84.9) |
| \textit{BRCA} mutations without family history of ovarian and/or breast cancer | 41 (20.2)\(^c\) |
| \(P\)                                                      | < .0001                         |

Abbreviation: VUS, variants of uncertain significance.

\(^a\)Patients with VUS having \textit{BRCA1} mutations were not included. There were four patients with \textit{BRCA1} VUS mutations.

\(^b\)Patients with VUS having \textit{BRCA2} mutations were not included. There were six patients with \textit{BRCA2} VUS mutations.

\(^c\)Percentage was calculated on the basis of the total number of participants available within each level.
frameshift, loss of function, and founder mutation in the Ashkenazi Jewish population and has also been reported in previous Indian studies with variable frequency. These patients were not of Ashkenazi Jewish descent and did not belong to any single geographical region in India. Among patients with a BRCA2 mutation, the commonest mutation was c.5851_5854del, which was reported in two unrelated patients and, to our knowledge, has not been reported in previous Indian studies.

Table 4 summarizes selected previous reports from India and other countries, in patients with ovarian cancer. The prevalence of germline pathogenic or likely pathogenic BRCA1/2 mutations in patients not selected by family history or histology ranged from 14.1% to 30.1%, and in previous reports selecting patients with relevant family history, it ranged from 38.7% to 100%. In previous reports of patients with serous histology, the prevalence of germline pathogenic or likely pathogenic BRCA1/2 mutations ranged from 16.6% to 97.14%. Our results do not show any notable outliers compared with what has been reported by others. Another incidental finding in our study is that 36 of 182 (19.8%) patients who had received ≤1 line of treatment had germline pathogenic or likely pathogenic mutation, whereas 15 of 57 (26.3%) patients receiving ≥2 lines of treatment had germline pathogenic or likely pathogenic mutation. This finding needs to be evaluated further since ours is a cross-sectional study. It is possible that patients who survive long enough to receive multiple lines of treatment are enriched for BRCA mutations, which is known to confer sensitivity to repeated courses of chemotherapy, as has also been reported earlier.

The strength of our analysis is inclusion of patients from multiple centers in India, of all age in the adult group, of all histologic subtypes, and those with or without relevant family history. This makes the results of this study generalizable to the patient population with ovarian cancer seen in routine practice in India. These study results can be used by physicians to counsel patients about the need for germline testing. Germline testing was performed in a single laboratory with a proven record of quality control. BRCA mutation testing in ovarian cancer offers prognostic ability and therapeutic decision making from the perspective of patient. BRCA mutation status can guide the use of poly(ADP ribose) polymerase inhibitors, which are associated with favorable outcomes in patients with BRCA mutations. Patients with germline mutations act as a proband for further testing of first-degree relatives (cascade screening). In this context, the results of this study reinforce recently published Indian guidelines, which recommend genetic

**TABLE 3. Distribution of BRCA Mutations (including VUS) With Age**

| Age (years) | All Enrolled | BRCA1 | BRCA2 | BRCA1 VUS | BRCA2 VUS |
|------------|-------------|-------|-------|-----------|-----------|
|            | All (%)     | No. (%) | No. (%) | No. (%) | No. (%) |
| All patients | 239 37 (15.5) | 14 (5.9) | 4 (1.7) | 6 (2.5) |
| ≤ 50 | 90 15 (16.7) | 5 (5.6) | 2 (2.2) | 0 (0.0) |
| > 50 | 149 22 (14.8) | 9 (6.0) | 2 (1.3) | 6 (4.0) |

**Abbreviation:** VUS, variants of uncertain significance.

**Percentage was calculated on the basis of the total number of participants available within each level. No significant association between pathogenic or likely pathogenic BRCA1/2 mutations and patients’ age was observed (P = .7956).**
testing in all patients with ovarian cancer and discuss the potential therapeutic and familial impact and likely challenges in the Indian context.\textsuperscript{35}

There are some limitations of our study. Although the study was designed to include patients not selected by clinical features, it is difficult to establish that the included set is representative of the entire ovarian cancer population without access to the clinical and pathologic characteristics of the latter. Moreover, because India is a diverse country with many regions having populations of distinct genetic background, it is not certain that our sample captures this diversity. One exclusion criterion in our study was participation in any other research study, which could have introduced a selection bias. However, this is unlikely to be an important consideration because there were no ongoing clinical trials for BRCA mutation–positive patients at the participating sites during the recruitment period. We are unable to correlate the prevalence of BRCA mutations with sensitivity to chemotherapy because this was beyond the scope of this study. From a technical standpoint, copy number variations were not evaluated in this study, either as part of the analytical pipeline of NGS data\textsuperscript{36} or by multiplex ligation-dependent probe amplification technique, which could have resulted in some underestimation of pathogenic alterations in \textit{BRCA1} and \textit{BRCA2}, especially large genetic rearrangements. Despite these limitations, our results provide valuable information relevant to the scope and need for germline testing in patients with ovarian, fallopian tube, or primary peritoneal cancers in India.

In conclusion, our results, in a cohort of Indian patients with epithelial ovarian, primary peritoneal, or fallopian tube cancers, suggest a high prevalence of germline pathogenic or likely pathogenic \textit{BRCA1}/\textit{2} mutations with no association with age. Evaluation of germline mutations in \textit{BRCA1} and \textit{BRCA2} should be considered in most patients with this disease.

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APPENDIX

Patients screened (N = 242)
Women age > 18 years with a current or previous diagnosis of ovarian, primary peritoneal, or fallopian tube cancer
Patients who provide written informed consent

Recruitment from March to December 2018 from nine sites

Total patients enrolled and assessed (n = 239)
(full analysis set)

Visit 1
Informed consent form
Eligibility criteria
Demographic data
Physical examination
Vital signs
Present or past history of illness
Family history of breast and/or ovarian cancer and current and previous chemotherapy regimen

Visit 2
Devolution of test results

Three participants dropped out—two not fulfilling inclusion criteria and one duplicate enrollment

FIG A1. Study flow.
| Site No. | Principal Investigator Name | Site Name and Address | City       |
|---------|----------------------------|-----------------------|------------|
| 1       | Dr Sudeep Gupta            | Tata Memorial Centre, Tata Memorial Hospital, Dr Ernest Borges Marg, Parel, Mumbai 400012 | Mumbai     |
| 2       | Dr Senthil Rajappa         | Basavataramakam Indo American Cancer Hospital & Research Institute, Road No 10, Banjara Hills, Hyderabad 500034 | Hyderabad  |
| 3       | Dr S. H. Advani            | Sushrut Hospital, 365 Swastik Park, Eastern Express Highway, Chembur East, Mumbai 400071 | Mumbai     |
| 4       | Dr Amit Agarwal            | Dr B. L. Kapur Hospital, Department Of Medical Oncology, OPD-7, First Floor, Pusa Road, New Delhi 110005 | New Delhi  |
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| 6       | Dr Chanchal Goswami        | Medica Superspecialty Hospital, 127, Mukundapur, EM Bypass, Kolkata 700099 | Kolkata    |
| 7       | Dr Satya Dattatreya Palanki| Omega Hospitals, MLA Colony, Main Road, Road No. 12, Anjata Hills, Hyderabad 500034, Telangana, India | Hyderabad  |
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NOTE. Tertiary care centers with a high volume (> 50 patients with ovarian cancer/year) of patients with ovarian cancer were included.
### TABLE A2. Participants With BRCA1 and BRCA2 Gene Mutations

| Age, years | Variation | Zygosity | Inheritance | Clinical Significance |
|------------|-----------|----------|-------------|----------------------|
| 45         | Chr17: 41243480_41243483deltgac... P.Asn1355lysfster10 | Heterozygous Dominant | Pathogenic |
| 72         | Chr17: 41242986_41242990delaggac... P.Ser1387glufster2 | Heterozygous Dominant | Pathogenic |
| 52         | Chr17: 41219624c... Heterozygous Dominant | Pathogenic |
| 48         | Chr17: 41243794_41243795delaggac... P.Leu1252valfster2 | Heterozygous Dominant | Pathogenic |
| 56         | Chr17: 41244567_41244568delca C.2981... P.Cys994ter | Heterozygous Dominant | Pathogenic |
| 43         | Chr17: 41226471delg C.4552delc P.Gln1518argfster30 | Heterozygous Dominant | Likely pathogenic |
| 56         | Chr17: 41234419a... Heterozygous Dominant | Pathogenic |
| 53         | Chr17: 41245253delt C.2295delt P.Ser766valfster26 | Heterozygous Dominant | Likely pathogenic |
| 43         | Chr17: 41215912... Heterozygous Dominant | Pathogenic |
| 56         | Chr17: 41219664delg C.5035delt P.Leu1679ter | Heterozygous Dominant | Pathogenic |
| 39         | Chr17: 41243779... Heterozygous Dominant | Pathogenic |
| 36         | Chr17: 41276047... Heterozygous Dominant | Pathogenic |
| 43         | Chr17: 41215948... Heterozygous Dominant | Likely pathogenic |
| 47         | Chr17: 41246360delt C.1188delt P.Asp96glufster14 | Heterozygous Dominant | Pathogenic |
| 42         | Chr17: 41244562delt C.2990delt P.Asn977deltfster3 | Heterozygous Dominant | Pathogenic |
| 54         | Chr17: 41246615delt C.933delt P.Gly312alafster2 | Heterozygous Dominant | Pathogenic |
| 53         | Chr17: 41276034... Heterozygous Dominant | Pathogenic |
| 46         | Chr17: 41243941g... Heterozygous Dominant | Pathogenic |
| 54         | Chr17: 41251792... Heterozygous Dominant | Pathogenic |
| 52         | Chr17: 41244321... Heterozygous Dominant | Pathogenic |
| 53         | Chr17: 41203127c... Heterozygous Dominant | VUS |
| 39         | Chr17: 41246360delt C.1188delt P.Asp96glufster14 | Heterozygous Dominant | Pathogenic |
| 52         | Chr17: 41246539dupo... Heterozygous Dominant | Pathogenic |
| 60         | Chr17: 41246538dupc C.1009dupg P.Glu337glufster9 | Heterozygous Dominant | Pathogenic |
| 37         | Chr17: 41245210g... Heterozygous Dominant | Pathogenic |
| 54         | Chr17: 41267755delt C.122delt P.His41profster9 | Heterozygous Dominant | Pathogenic |
| 67         | Chr17: 41249261... Heterozygous Dominant | Pathogenic |
| 56         | Chr17: 41215970delt C.5075-2dela | Heterozygous Dominant | Pathogenic |
| 58         | Chr17: 41267743... Heterozygous Dominant | Pathogenic |

(Continued on following page)
| Age, years | Variation | Zygosity | Inheritance | Clinical Significance |
|------------|-----------|----------|-------------|----------------------|
| 53         | Chr17: 41276047_41276048delct C.68_69delag P.Glu23valfster17 | Heterozygous | Dominant | Pathogenic |
| 63         | Chr17: 41276047_41276048delct C.68_69delag P.Glu23valfster17 | Heterozygous | Dominant | Pathogenic |
| 55         | Chr17:41219669_41219672deltg Ta C.5030_5033delctaa P.Thr1677ilefster2 | Heterozygous | Dominant | Pathogenic |
| 53         | Chr17: 41258533_a.g C.152t.c P.Leu51pro | Heterozygous | Dominant | VUS with probable damaging effect (VUSd)* |
| 59         | Chr17: 41245281delc C.2269delg P.Val757phefster8 | Heterozygous | Dominant | Pathogenic |
| 50         | Chr17: 41267746c.t C.131g.a P.Cys44tyr | Heterozygous | Dominant | Likely pathogenic |
| 44         | Chr17:41234420c->g C.4357+1g>c | Heterozygous | Dominant | Likely pathogenic |
| 47         | Chr17:41245170_41245171duptt C.2377_2378dupaa P.Ala794argfster10 | Heterozygous | Dominant | Likely pathogenic |
| 52         | Chr17: 41228619g>c C.4370c>g P.Ser1457ter | Heterozygous | Dominant | Pathogenic |
| 29         | Chr17: 41243921dup C.3627dupa P.Glu1210argfster9 | Heterozygous | Dominant | Pathogenic |
| 43         | Chr17: 41215932a.g C.5111t.c P.Phe1704ser | Heterozygous | Dominant | VUS |
| 59         | Chr17: 41243680_41243681deltt C.3869_3870delaa P.Lys1290metfster4 | Heterozygous | Dominant | Pathogenic |

Participants with BRCA2 gene mutations detected

| Age, years | Variation | Zygosity | Inheritance | Clinical Significance |
|------------|-----------|----------|-------------|----------------------|
| 58         | Chr13: 32914343_32914346delagtttc.5851_5854delagtttc.P.Ser1951trpfster11 | Heterozygous | Dominant | Pathogenic |
| 61         | Chr13: 32968949g>a C.9380g>a P.Trp3127ter | Heterozygous | Dominant | Pathogenic |
| 49         | Chr13: 32954050c->a C.9117g>a P.Pro3039pro | Heterozygous | Dominant | Pathogenic |
| 61         | Chr13: 32929379_32929382deltc Aa|c.7389_7392deltcaalp.Asn2463lysfsfster3 | Heterozygous | Dominant | Pathogenic |
| 67         | Chr13: 32913132delac.4631delal p.Asn15444thrfsfster24 | Heterozygous | Dominant | Pathogenic |
| 56         | Chr13: 32910551_32910555delga Tta C.2059_2063delagta P.Asp687ter | Heterozygous | Dominant | Pathogenic |
| 58         | Chr13: 32914723g>c C.6231g>c P.Lys2077asn | Heterozygous | Dominant | VUS |
| 62         | Chr13: 32969027delgc.9458delgc p.Gly3153alaafsster10 | Heterozygous | Dominant | Pathogenic |
| 52         | Chr13: 32915179a.g C.6687a.g P.Glu2229asp | Heterozygous | Dominant | VUS |
| 52         | Chr13: 32913530_32913531deins Aa C.5038_5039deins Aa P.Ser1680105-004 | Heterozygous | Dominant | VUS |
| 55         | Chr13: 32912001c>t C.3509c>t P.Ala1170val | Heterozygous | Dominant | VUS |
| 57         | Chr13:32914514a>c C.6022a>c P.Lys2008ter | Heterozygous | Dominant | Pathogenic |
| 54         | Chr17: 41276047_41276048delct C.68_69delag P.Glu23valfster17 | Heterozygous | Dominant | Pathogenic |
| 47         | Chr13: 32953482c>t C.8783c>t P.Ala2928val | Heterozygous | Dominant | VUS |
| 72         | Chr13: 32914977a->g C.6485a->g P.Lys2162arg | Heterozygous | Dominant | VUS |
| 44         | Chr13: 32929398_32929399delttt C.7408_7409delttt P.Phe2470hisfsfster4 | Heterozygous | Dominant | Pathogenic |
| 48         | Chr13: 32954267delc.9241delgc P.Val3081ilefsfster2 | Heterozygous | Dominant | Likely pathogenic |

(Continued on following page)
| Age, years | Variation | Zygosity | Inheritance | Clinical Significance |
|------------|-----------|----------|-------------|----------------------|
| 45         | Chr13: 32911115_32911116delgt C.2623_2624delgt P.Val875IlefsTer5 | Heterozygous | Dominant | Pathogenic |
| 52         | Chr13: 32914343_32914346delag Tt C.5851_5854delagtt P.Ser1951trpfsTer11 | Heterozygous | Dominant | Pathogenic |
| 52         | Chr13: 32911578dup C.3086dup Met1029ilefsTer7 | Heterozygous | Dominant | Pathogenic |
| 58         | Chr13: 32945135g>a C.8530g>a P.Glu2844Lys | Heterozygous | Dominant | VUS |

Abbreviation: VUS, variant of uncertain significance.

*Considered as a VUS for the purpose of analysis.