MOLECULAR HEALTH
MH BRCA

Date of birth	—	Patient ID	—
Suspected disease	HBOC	ICD-10-CM	—

Case ID	—	Software version	—	Ordering physician	—
Ethnicity	—	General dataset ID	—	Email	—
Sex	Female	CVI dataset ID	—	Phone	—
Labtest	—	Collected	—	Fax	—
				Product	MH BRCA
				Report	—

Hereditary breast and ovarian cancer (HBOC)

A condition associated with familial predisposition to cancer of the breast and ovaries. Characteristic features in affected families are an early age of onset of breast cancer (often before age 50), increased chance of bilateral cancers (cancer that develop in both breasts, or both ovaries, independently), frequent occurrence of breast cancer among men, increased incidence of tumors of other specific organs, such as the prostate (definition from www.uniprot.org).

Analyzed genes

The following genes were considered for analysis: ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MSH2, MLH1, MSH6, PMS2, EPCAM, NBN, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53

Detected variants per classification

Pathogenic	Likely pathogenic	Uncertain significance	Likely benign	Benign	Unclassified
0	1	0	0	0	1

Detected pathogenic and likely pathogenic variants

Variant	Variant effect	Zygosity	Classification
BRCA1 ENST00000357654.3 c.5117G>A	Missense	heterozygous	Likely pathogenic

Cancer risk of pathogenic variants per gene

Standard medical guidelines and studies indicate that pathogenic variants located on the genes listed here are associated with HBOC predisposition. The increased disease risk is independent of variant zygosity. A homozygous variant means the disease risk is passed on to the next generation. For heterozygous variants, disease inheritance is uncertain. The cancer risk per gene can be uncertain, potentially increased, or increased.

Gene	Breast cancer risk	Ovarian cancer risk	Other increased cancer risks	Source
ATM	Increased	Potentially increased	No data available	NCCN
BARD1	Potentially increased	Uncertain	No data available	NCCN
BRCA1	Increased	Increased	Prostatic neoplasms	NCCN
BRCA2	Increased	Increased	Melanoma; Pancreatic neoplasms; Prostatic neoplasms	NCCN
BRIP1	Uncertain	Increased	No data available	NCCN
CDH1	No data available	No increase	Stomach neoplasms; Carcinoma, lobular	NCCN
CHEK2	Increased	No increase	Colorectal neoplasms	NCCN
EPCAM	Uncertain	Increased	Colorectal neoplasms; Endometrial neoplasms	NCCN
MLH1	Uncertain	Increased	Endometrial neoplasms; Colorectal neoplasms	NCCN
MSH2	Uncertain	Increased	Endometrial neoplasms; Colorectal neoplasms	NCCN
MSH6	Uncertain	Increased	Endometrial neoplasms; Colorectal neoplasms	NCCN

NBN	Increased	Uncertain	No data available	NCCN
NF1	Increased	No increase	No data available	NCCN
PALB2	Increased	Uncertain	No data available	NCCN
PMS2	Uncertain	Increased	Colorectal neoplasms	NCCN
PTEN	Increased	No increase	Colorectal neoplasms	NCCN
RAD51C	Uncertain	Increased	No data available	NCCN
RAD51D	Uncertain	Increased	No data available	NCCN
STK11	Increased	No data available	Sex cord-gonadal stromal tumors; Neoplasms, germ cell and embryonal; Colorectal neoplasms	NCCN
TP53	Increased	No increase	Colorectal neoplasms	NCCN

Detected variants

This section provides details on all detected variants matching the filter criteria.

Variant: Protein	Variant: Coding DNA	Variant: Genomic	Variant effect	Zygosity	Classification
BRCA1 (p.G1706E)	ENST00000357654.3 c.5117G>A	chr17 g.41215926C>T	Missense	Het	Likely pathogenic
CDH1	ENST00000261769.5 c.833-32G>A	chr16 g.68845555G>A	Non-coding	Het	Unclassified

Molecular Health glossary

Classification:
The variants listed can either be unclassified or they can be assigned to an ACMG classification. ACMG classifications of variants can be Pathogenic, Likely pathogenic, Uncertain significance, Likely benign, or Benign. Source: Richards S., Aziz N., Bale S., Bick D., Das S., Gastier-Foster J., Grody W.W., Hegde M., Lyon E., Spector E., Voelkerding K., Rehm HL.; ACMG Laboratory Quality Assurance Committee "Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, " Genetics in Medicine, vol. 17, issue 5, pp. 405-24, 2015, doi: 10.1038/gim.2015.30.

Inheritance:
The inheritance type of a disease describes the circumstances under which a disease is passed from one generation to the next. Diseases with a dominant inheritance type are always passed on to the next generation, while diseases with a recessive type may not be passed on, if only a heterozygous variant associated with the disease is detected.

Zygosity:
The zygosity of a variant can be homozygous, heterozygous, or hemizygous. Homozygous and hemizygous means the variant was detected on all copies of the gene, heterozygous means the variant was detected on only one of the copies of the gene, and one healthy copy of the gene is still present. Zygosity tells you more about the inheritance type of the variant.

Molecular Health disclaimer

Molecular Health Guide BRCA (MH BRCA) is a bioinformatics software for the annotation of genetic data from genes associated with hereditary breast and ovarian cancer. It provides variant annotation data to support physicians in classifying variants and storing variant classifications for future cases. It enables medical experts to generate a customizable clinical report that includes a list of annotated variants they identified as clinically relevant, a conclusion explaining the reasoning behind this decision, and a list of analyzed genes for which pathogenic variants are known to be associated with hereditary breast and ovarian cancer.

MH BRCA covers:

1. Identification and processing of a patient's genetic alterations in the genes associated with hereditary breast and ovarian cancer.
2. Aggregation, integration, collation, and maintenance of up-to-date biomedical reference information.
3. Mapping of the patient's genetic alterations to the biomedical reference information.
4. Integration and pre-classification of the patient's genetic alterations based on the mapping to biomedical reference information.
5. Generation of a customizable clinical report by a trained user or MH-certified physician.

The information consolidated into the clinical report is the result of comprehensive filter settings based on values defined by the MH-certified physician. The MH-certified physician is neither a contractor nor an employee of MH. The information provided in the report must be evaluated in conjunction with all other relevant clinical information of the patient.

The information provided in this disclaimer may not be applicable when the product is used in other configurations than the MH standard configuration.

The contents of the clinical report, a result of mapping and pre-classification of patient data against the MH database, followed by a final classification by the MH-certified physician, are for use only as additional assistance for diagnosing. Interpretation of the report contents must occur in consultation with a medical expert. Decisions on patient diagnosis, care, and treatment must be based on independent medical judgment, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the applicable standard of care. Decisions regarding diagnosis, care, and treatment should not be based solely on the information contained in this report.

The identification of a genomic alteration does not necessarily imply a definite diagnosis. Also, the absence of a reported diagnosis does not necessarily invalidate a suspected diagnosis.

The following phenotypes are excluded from the intended use: blood groups; infections and infectious diseases; irregular anti-erythrocytic antibodies; the hereditary disease phenylketonuria; the HLA tissue groups DR, A, and B; the tumoral marker PSA, and the risk of trisomy 21.

MH BRCA supports detection and annotation of single nucleotide variants (SNVs), insertions, deletions, and indels from FASTQ or VCF data. When reports are generated from VCF data, also reporting of copy number alterations (CNAs) and fusions is possible.

The quality of the results from MH BRCA depends on the quality of the input data submitted by a lab on behalf of the MH-certified physician. For VCF input, the accuracy, analytic sensitivity, and specificity of the variant lists is the sole responsibility of the MH-certified physician. For FASTQ the accuracy, analytic sensitivity, and specificity of the variant lists is can only be guaranteed when standards from MH sequencing guidelines are adhered to.

For ethnicity Japanese (JPT) a population-specific reference genome based on ToMMo 3.5KJPNv2 (MAF>=1%) is used for sequencing alignment. Additionally, population frequencies from ToMMo 3.5KJPNv2 (MAF>=1%) are available in the application for display and filtering.

MH BRCA uses and contains data and information obtained from third-party sources. Molecular Health GmbH (MH) uses reasonable efforts to ensure that this information is as accurate as possible in a tightly controlled QA process. However, MH cannot guarantee that data from any third party are accurate, comprehensive, and complete. Thus, MH BRCA may not contain all relevant or all up-to-date information. Third-party databases or other sources in MH BRCA may only be updated from time to time with new or revised information.

MH BRCA has not been cleared or approved by the U.S. Food and Drug Administration (FDA). However, MH BRCA using VCF as input is offered as a bioinformatics service under CLIA.
In the European Union, MH BRCA is a subcomponent of MH Guide, which is registered as an in vitro diagnostic medical device (IVD).

MH is the legal manufacturer of MH BRCA as a stand-alone software, the statutory provisions of the German Medical Devices Act (MPG) and the European Directive 98/79/EC apply to MH. We therefore maintain a quality management system according to EN ISO 13485 for the scope of "Design, Development and Manufacture of software systems for the integrated analysis of clinical and genomic patient data to support treatment decisions and provision of related services." MH has also received CLIA certification and CAP accreditation for the provision of MH BRCA as a dry lab service to clinical laboratories in the US.

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