ASPIRA GENETIX
BY ASPIRA LABS

Risk Assessment
Jane Doe

PATIENT INFORMATION
Last Name: Doe
First Name: Jane
MRN: MRN12345
DOB: 03/07/1983
Age: 38
Gender: Female
Ethnicity: Other
Indication: ICD10 Diagnosis Code(s),Personal History,Family History

PROVIDER INFORMATION
Ordering Provider:
Practice Name:
Steet Address:
Copy-to-physician:
Fax:

LAB INFORMATION
Accession No: GX12345678901
Collection Date:
Received Date:
Final Report Date:

POSITIVE

PATHOGENIC *BRCA1* Variant Detected

- The lifetime risk for ovarian cancer has been estimated at 44-54%.
- The highest cancer risk associated with this finding is an up to 87% lifetime risk for breast cancer.
- This finding may also be associated with an increased risk for serous uterine cancer and melanoma, although that risk has not yet been sufficiently quantified.

Clinical Management Recommendation Summary:[8]

- Annual clinical breast exams should begin for women at age 25 years. Annual breast MRI screening with contrast is recommended for women from 25-29 years followed by annual mammogram with consideration of tomosynthesis and breast MRI starting at age 30 years.
- Discuss the option of risk-reducing salpingo-oophorectomy and risk-reducing mastectomy.
- For pancreatic cancer, screening may be individualized based on cancers in the family history.
- Genetic counseling is recommended

Gene	OMIM	Change	Zygosity	Classification
BRCA1	113705	c.1852_1853delinsGC (p.K618A)	heterozygous	pathogenic

Lifetime Cancer Risk by Cancer Type

Lifetime cancer risks (70-80 years of age) [BRCA1 [1-7]] and associated Clinical Management Recommendations for Pathogenic/Likely Pathogenic variants are listed below. The Lifetime Cancer Risk and Management Recommendations contained in this report are provided for clinician reference only. Aspira does not directly provide any recommendations for management and/or treatment. Aspira is not responsible for management and/or treatment decisions made based on recommendations contained in this report.

Electronically Signed by: Dr. Christine M. Eng, M.D. on 01/07/2021 at 11:39 AM
Electronically Signed by: Dr. Jennifer Scull, Ph.D. on 01/07/2021 at 11:39 AM

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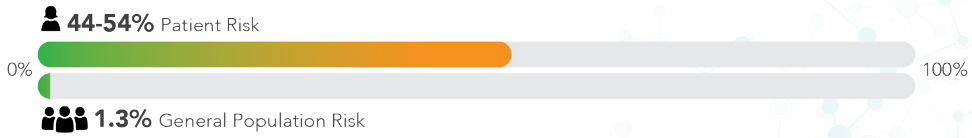
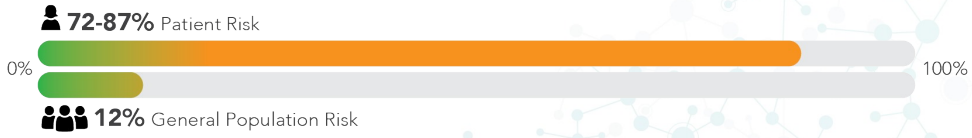


Ovarian Cancer

You have an up to **41x** increased risk



Female Breast Cancer

You have an up to **7.25x** increased risk

Pancreatic Cancer

You have an up to **4x** increased risk

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Clinical Management Recommendations

All management recommendations [BRCA1[8]] are referenced from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) unless otherwise indicated.

Ovarian cancer

Recommendation	Age to Begin	Frequency
Consider risk-reducing salpingo-oophorectomy (RRSO) after child-bearing is complete	35-40 years	
If ovaries have not been removed, consider transvaginal ultrasound with CA-125 based on clinician's discretion (benefit of these tests is unknown)	35 years	Annual

Female breast cancer

Recommendation	Age to Begin	Frequency
Clinical breast exam	25 years	6 - 12 months
Breast MRI screening with contrast	25-29 years or earlier if breast cancer diagnosis in the family before age 30 is present	Annual
Mammogram with consideration of tomosynthesis and breast MRI with contrast	30-75 years; Individualized management >75 years	Annual
Discuss option of risk-reducing mastectomy (RRM)		

Pancreatic cancer

Recommendation	Age to Begin	Frequency
Individuals with at least 1 first or second degree relative with pancreatic cancer may consider screening by MRI, MRCP (magnetic resonance cholangiopancreatography) and/or endoscopic ultrasound	50 years or earlier based on family history of pancreatic cancer	Annual

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Additional Information

Clinical Interpretation

BRCA1 c.1852_1853delinsGC (p.K618A)

A heterozygous pathogenic variant, c.1852_1853delinsGC (p.K618A) in the BRCA1 gene, was detected.

Gene Description

The BRCA1 gene encodes a tumor suppressor that is involved in maintaining genome stability through coordination of various aspects of DNA double strand break repair. Heterozygous pathogenic variants in the BRCA1 gene are associated with increased risks of breast, ovarian, prostate, and pancreatic cancer (OMIM: 604370; GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1247/). Biallelic germline pathogenic variants in the BRCA1 gene are associated with Fanconi anemia, complementation group S (OMIM: 617883).

Glossary

Pathogenic variant: A change in DNA that is considered by this laboratory to be associated with an increased risk for disease.

Likely pathogenic variant: A change in DNA that is considered by this laboratory to have high, although not complete, certainty to be associated with anincreased risk for disease.

Variant of uncertain significance (VUS): There is insufficient data available for these variants to classify them as either pathogenic or benign, as clinical significance remains unknown.

References

BRCA1

1. Ford, D., Easton, D. F., Bishop, D. T., Narod, S. A., & Goldgar, D. E. (1994). Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *Lancet (London, England)*, 343(8899), 692–695. https://doi.org/10.1016/s0140-6736(94)91578-4

2. Kuchenbaecker, K. B., Hopper, J. L., Barnes, D. R., Phillips, K. A., Mooij, T. M., Roos-Blom, M. J., Jervis, S., van Leeuwen, F. E., Milne, R. L., Andrieu, N., Goldgar, D. E., Terry, M. B., Rookus, M. A., Easton, D. F., Antoniou, A. C., BRCA1 and BRCA2 Cohort Consortium, McGuffog, L., Evans, D. G., Barrowdale, D., Frost, D., … Olsson, H. (2017). Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA*, 317(23), 2402–2416. https://doi.org/10.1001/jama.2017.7112

3. Feuer, E. J., Wun, L.-M., Boring, C. C., Flanders, W. D., Timmel, M. J., & Tong, T. (1993). The Lifetime Risk of Developing Breast Cancer. *JNCI Journal of the National Cancer Institute*, 85(11), 892–897. https://doi.org/10.1093/jnci/85.11.892

4. Pilarski R. (2019). The Role of BRCA Testing in Hereditary Pancreatic and Prostate Cancer Families. American Society of Clinical Oncology educational book. *American Society of Clinical Oncology. Annual Meeting*, 39, 79–86. https://doi.org/10.1200/EDBK_238977

5. Cancer of the Pancreas - Cancer Stat Facts. (2018). Retrieved from SEER website: https://seer.cancer.gov/statfacts/html/pancreas.html

6. Ramus, S. J., & Gayther, S. A. (2009). The contribution of BRCA1 and BRCA2 to ovarian cancer. *Molecular oncology*, 3(2), 138–150. https://doi.org/10.1016/j.molonc.2009.02.001

7. The American Cancer Society. Key Statistics for Ovarian Cancer. (2019). Retrieved from Cancer.org website: https://www.cancer.org/cancer/ovarian-

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cancer/about/key-statistics.html

8. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic V.2.2021. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Last Accessed [September 4th, 2020]. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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Methods and Limitations

The targeted regions in this panel are enriched using a capture-based method and sequenced using the Illumina platform. Nucleotide 1 corresponds to the A of the start codon ATG. Variants detected in exons and within 20 bp of the exon/intron boundary are reported, unless otherwise specified. Overall, more than 99% of targeted regions are sequenced. Read depth analysis is used to detect copy number variation (CNV) for genes in this panel. This analysis will not detect variants within promoter or deep intronic regions (unless otherwise specified), balanced translocations, inversions (unless otherwise specified),low-level mosaicism, uniparental disomy, and imprinting defects. Single exon duplications will not be analyzed or reported unless otherwise specified. Positive sequencing results from certain genes or regions with highly homologous sequences in the genome will be confirmed by gene-specific long-range PCR and Sanger sequencing of the amplification products. Multiplex ligation-dependent probe amplification (MLPA), PCR-based methods, and/or array comparative genomic hybridization (aCGH) may be used to confirm copy number changes involving the genes in this panel. Certain genes or regions with highly homologous sequences in the genome will be evaluated, but 100% coverage by the above analyses are not guaranteed due to genetic complexity.

Note that next-generation sequencing-based CNV analysis can be impacted by sample quality, DNA input, characteristics of targeted regions (GC content, presence of homologous sequences, etc.), and other technical variations. Read depth analyses that are either uninformative or unsupportive of a copy number change may not exclude large deletions or duplications. Findings are reported according to the human genome build hg19.

SPECIAL NOTES: For the EPCAM gene, only cancer-related copy number changes will be analyzed and reported.

Variants that have been classified as pathogenic, likely pathogenic and of uncertain significance are reported per our internal classification methods. Our laboratory's variant classification criteria are based on the American College of Medical Genetics and Genomics (ACMG), internal guidelines, and our current understanding of the specific genes. If the majority of available information suggests the variant has no clinical significance it is not reported. This interpretation may change over time as more information about a gene and/or variant becomes available. Most silent variants or known polymorphisms are likely benign; however, we cannot exclude the possibility of their interference with precursor RNA processing. Missense polymorphisms may also have effects on disease predisposition or may be synergistic for disease expression. Possible diagnostic errors include sample mix-ups, interfering substances, genetic variants that interfere with analysis, incorrect assignment of biological parentage, history of bone marrow transplant, and other sources. Please contact Natera if there is reason to suspect one of these sources of error.

Sequence analysis is based on the following gene transcripts: ATM (NM_000051), BARD1 (NM_000465), BRCA1 (NM_007294), BRCA2 (NM_000059), BRIP1 (NM_032043), CDH1 (NM_004360), CHEK2 (NM_007194), DICER1 (NM_177438), EPCAM (NM_002354), FANCC (NM_001243744.1), MLH1 (NM_000249), MRE11 (NM_005591), MSH2 (NM_000251), MSH6 (NM_000179), MUTYH (NM_001128425), NBN (NM_002485), NF1 (NM_000267), NTHL1 (NM_002528), PALB2 (NM_024675), PMS2 (NM_000535), POLD1 (NM_002691), POLE (NM_006231), PTEN (NM_000314), RAD50 (NM_005732), RAD51C (NM_058216), RAD51D (NM_002878), SDHB (NM_003000), SDHD (NM_003002), SMARCA4 (NM_003072), STK11 (NM_000455), TP53 (NM_000546), WRN (NM_000553.4), XRCC2 (NM_005431).

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Genes Analyzed:

ATM	***DICER1***	***MUTYH***	***POLE***	***SMARCA4***
BARD1	***EPCAM***	***NBN***	***PTEN***	***STK11***
BRCA1	***FANCC***	***NF1***	***RAD50***	***TP53***
BRCA2	***MLH1***	***NTHL1***	***RAD51C***	***WRN***
BRIP1	***MRE11***	***PALB2***	***RAD51D***	***XRCC2***
CDH1	***MSH2***	***PMS2***	***SDHB***	
CHEK2	***MSH6***	***POLD1***	***SDHD***	

Disclaimer: This test was developed and its performance characteristics determined by Baylor Miraca Genetics Laboratories DBA Baylor Genetics (CAP# 2109314 / CLIA# 45D0660090; Lab Director: Christine M. Eng, MD). It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigation or for research. Report content included in the results summary, lifetime cancer risk, and management recommendations is provided by Aspira Women's Health, Inc. and is provided for clinician convenience only. Aspira does not provide any recommendations for clinical management or treatment. Clinicians are solely responsible for obtaining information necessary to make management and/or treatment decisions. Aspira is not responsible for management and/or treatment decisions made based on recommendations contained in this report. The remaining content is developed by Baylor Genetics.