BRCAsomatic

Clinical Testing
Cert. No. 822

Genekor Medical S.A. | 52, Spaton Ave., 15344, Gerakas, Athens, Greece, , G.E.MI. nr: 0007856001000
email: info@genekor.com, www.genekor.com | Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

SAMPLE INFORMATION

Name :		**Date Received :**	
Medical ID :		**Date of Report :**	
Date of Birth :		**Req. Physician :**	
Material :	PARAFFIN EMBEDDED TISSUE	**Barcode :**	
Code of sample :		**Tumor type**	Ovarian Cancer

Somatic mutation analysis of the *BRCA1* and *BRCA2* genes

Result

***BRCA1* - No known pathogenic mutation or rearrangement was identified in the patient's tumor tissue**

BRCA2*- *Deletion of entire gene

Large genomic rearrangements, including deletions, duplications or insertions larger than 500 kb, have been identified in the BRCA1/2 genes, with a frequency between 0 and 28% depending on the population analyzed (PMID: 26271414, 20232141, 22434521, 22544547, 28212807). The variant detected in this patient is a deletion of the entire BRCA2 gene. It was identified by NGS and confirmed by MLPA (Multiplex Ligation dependent Probe Amplification, MRC Holland; PMID: 10978226). BRCA2 gene deletion has been reported to be inactivating. Loss of BRCA2 has been demonstrated to cause a significant increase in genome-wide error-prone repair of both spontaneous DNA damage and mitomycin C-induced DNA cross-links(PMID: 11532935). To our knowledge, this particular variant has not been described in literature or mutation database ClinVar. However, BRCA2 deletions have been reported in international literature (PMID: 29570666, 16199546, 32375709) and in ClinVar mutation database as pathogenic. For these reasons this variant is predicted to be pathogenic. Analysis of patient's blood is recommended in order to determine the germline or somatic origin of this alteration.

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Methodology

Mutations in the *BRCA1* and *BRCA2* genes lead to an increased risk of developing breast or ovarian cancer as part of hereditary breast-ovarian cancer syndrome. Recent studies have established that these genes can also be involved in the development of non-hereditary, sporadic tumors, since a proportion of ovarian, breast cancer and prostate cancer tumors contain somatic (tumor only) *BRCA1* and *BRCA2* pathogenic variants. Patients with tumors that harbor a somatic BRCA mutation may benefit from treatment with PARP inhibitors.

Genomic DNA was extracted from the FFPE tumor tissue. Analysis was carried out using the commercially available Oncomine BRCA assay (Thermo Fisher Scientific). Sequencing was carried out using the Next Generation Sequencing platform Ion GeneStudio™ S5 Prime System (Thermo Fisher Scientific). The presence of large genomic rearrangements is investigated by use of the method MLPA (Multiplex Ligation-dependent Probe Amplification, BRCA1: P002, BRCA2: P045, MRC Holland; AJHG 67:841-50, 2000).

*Notes:

[1] Macrodissection was performed on the cancerous tissue

[2] Large genomic rearrangement analysis when performed in FFPE tissue has lower sensitivity compared to whole peripheral blood

[2] Each molecular analysis has an internal error probability of 0,5-1%. This is due to rare molecular events and factors involved in the production and analysis of specimens.

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References

1. Hennessy BT, Timms KM, Carey MS, Gutin A, Meyer LA, Flake DD 2nd, Abkevich V, Potter J, Pruss D, Glenn P, Li Y, Li J, Gonzalez-Angulo AM, McCune KS, Markman M, Broaddus RR, Lanchbury JS, Lu KH, Mills GB. **Somatic mutations in BRCA1 and BRCA2 could expand the number of patients that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer.** J Clin Oncol. 2010 Aug 1;28(22):3570-6. doi: 10.1200/JCO.2009.27.2997. Epub 2010 Jul 6. PMID: 20606085; PMCID: PMC2917312.
2. Watkins JA, Irshad S, Grigoriadis A, Tutt AN. **Genomic scars as biomarkers of homologous recombination deficiency and drug response in breast and ovarian cancers.** Breast Cancer Res. 2014 Jun 3;16(3):211. doi: 10.1186/bcr3670. PMID: 25093514; PMCID: PMC4053155.
3. Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, Nava Rodrigues D, Robinson D, Omlin A, Tunariu N, Boysen G, Porta N, Flohr P, Gillman A, Figueiredo I, Paulding C, Seed G, Jain S, Ralph C, Protheroe A, Hussain S, Jones R, Elliott T, McGovern U, Bianchini D, Goodall J, Zafeiriou Z, Williamson CT, Ferraldeschi R, Riisnaes R, Ebbs B, Fowler G, Roda D, Yuan W, Wu YM, Cao X, Brough R, Pemberton H, A Hern R, Swain A, Kunju LP, Eeles R, Attard G, Lord CJ, Ashworth A, Rubin MA, Knudsen KE, Feng FY, Chinnaiyan AM, Hall E, de Bono JS. **DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer.** N Engl J Med. 2015 Oct 29;373(18):1697-708. doi: 10.1056/NEJMoa1506859. PMID: 26510020; PMCID: PMC5228595.
4. Miller RE, Leary A, Scott CL, Serra V, Lord CJ, Bowtell D, Chang DK, Garsed DW, Jonkers J, Ledermann JA, Nik-Zainal S, Ray-Coquard I, Shah SP, Matias-Guiu X, Swisher EM, Yates LR. **ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer.** Ann Oncol. 2020 Dec;31(12):1606-1622. doi: 10.1016/j.annonc.2020.08.2102. Epub 2020 Sep 28. PMID: 33004253.
5. Riahi A et al. **Prevalence of BRCA1 and BRCA2 large genomic rearrangements in Tunisian high risk breast/ovarian cancer families: Implications for genetic testing.** Cancer Genet. 2017 Jan;210:22-27. doi: 10.1016/j.cancergen.2016.11.002. (PMID: 28212807)
6. Sluiter MD et al. **Large genomic rearrangements of the BRCA1 and BRCA2 genes: review of the literature and report of a novel BRCA1 mutation.** Breast Cancer Res Treat. 2011 Jan;125(2):325-49. doi: 10.1007/s10549-010-0817-z. (PMID: 20232141)
7. van der Merwe NC et al. **The contribution of large genomic rearrangements in BRCA1 and BRCA2 to South African familial breast cancer.** BMC Cancer. 2020 May 6;20(1):391. doi: 10.1186/s12885-020-06917-y. (PMID: 32375709)
8. Scaglione GL et al. **A Whole Germline BRCA2 Gene Deletion: How to Learn from CNV In Silico Analysis.** Int J Mol Sci. 2018 Mar 23;19(4):961. doi: 10.3390/ijms19040961. (PMID: 29570666)
9. Judkins T et al. **Clinical significance of large rearrangements in BRCA1 and BRCA2.** Cancer. 2012 Nov 1;118(21):5210-6. doi: 10.1002/cncr.27556. (PMID: 22544547)
10. Kwong A et al. **The importance of analysis of long-range rearrangement of BRCA1 and BRCA2 in genetic diagnosis of familial breast cancer.** Cancer Genet. 2015 Sep;208(9):448-54. doi: 10.1016/j.cancergen.2015.05.031. (PMID: 26271414)
11. Tutt A et al. **Mutation in Brca2 stimulates error-prone homology-directed repair of DNA double-strand breaks occurring between repeated sequences.** EMBO J. 2001 Sep 3;20(17):4704-16. doi: 10.1093/emboj/20.17.4704. (PMID: 11532935)
12. Agata S et al. **Large genomic deletions inactivate the BRCA2 gene in breast cancer families.** J Med Genet. 2005 Oct;42(10):e64. doi: 10.1136/jmg.2005.032789. (PMID: 16199546)
13. Ruiz de Garibay G et al. **Characterization of four novel BRCA2 large genomic rearrangements in Spanish breast/ovarian cancer families: review of the literature, and reevaluation of the** Breast Cancer Res Treat. 2012 May;133(1):273-83. doi: 10.1007/s10549-011-1909-0. (PMID: 22434521)