City of Hope™

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Assay Summary

BRCA1 and BRCA2

Hereditary Breast and Ovarian Cancer, Prostate Cancer, Pancreatic Cancer Susceptibility

Synopsis

Inherited breast cancer represents approximately 7% of all breast cancer[1]. Germline mutations in two major causal genes, *BRCA1* and *BRCA2*, account for up to 80% of strongly familial breast cancers. Mutations are inherited in an autosomal dominant manner, with high (though not complete) penetrance, and have been associated with 40-80% lifetime risk for breast, 11-40% for ovarian, up to 39% for prostate and up to 7% for pancreatic cancer[2-4]. Ethnic-specific mutations have also been identified; in particular three common founder mutations in individuals of Ashkenazi Jewish ancestry [c.68_69delAG (*BRCA1*), c.5266dupC (*BRCA1*), and c.5946delT (*BRCA2*)] account for the vast majority of BRCA1/2 associated hereditary breast cancers[5].

Genetic testing results in familial breast and ovarian cancers can influence medical care in guiding surveillance, management and providing ability to identify other at-risk family members.

Indications for testing

Individual with personal clinical and/or family history features suggestive of genetic predisposition to breast and/or ovarian cancer. If a mutation is identified in the patient, other at-risk family members may be tested for carrier status.

Methodology

Sequence analysis: Coding exons and associated intron junctions are captured and enriched using custom Agilent SureSelect technology. Next-generation sequencing is performed on Illumina MiSeq. Additional Sanger sequencing is performed for any regions with insufficient depth of coverage or for verification of suspect variant calls. Targeted testing for known familial sequence variant is performed by Sanger sequencing.

MLPA analysis for large deletions or duplications: Multiplex Ligation-Dependent Probe Amplification (MLPA, MRC-Holland) technology is used for detection of large deletions and duplications of one or more exons of the genes.

Targeted analysis of the BRCA1/2 Ashkenazi Jewish common mutations: Bi-directional amplification of specific alleles (Bi-PASA) is used to detect the Ashkenaki Jewish common mutations [c.68_69delAG (*BRCA1*), c.5266dupC (*BRCA1*), and c.5946delT (*BRCA2*)]

Limitations

The gene/s are not sequenced in their entirety (deep intronic and untranslated regions will not be analyzed). Sequencing will not detect gross genetic alterations including most large deletions, duplications, and inversions). MLPA does not determine precise breakpoints of alterations detected. MLPA analysis will not detect certain

genetic alterations, such as point mutations or small deletions/insertions and inversions. Additionally, MLPA analysis may be sensitive to DNA sample purity and other experimental conditions. Probe signals may also be adversely affected by sequence variants situated in the vicinity of, or at the probe ligation site; therefore, apparent deletions/duplications detected by a single probe should be confirmed by other methods. Partial exonic deletions/duplications outside of the probe target sequence may not be detected.

Some sequence alterations may be of unknown clinical significance. Interpretation of test results should be in the context of the patient's ethnicity, clinical and family histories, and other laboratory test results.

Specimen Requirements

Blood samples: 2 tubes with a total of 6 ccs in EDTA (lavender top) or ACD (yellow top) tubes.
Keep at ambient temperature and ship by overnight courier. Samples must be received in our laboratory within 72 hours of draw.

Note:

i) for infants, a minimum of 3 ccs is sufficient.
ii) we accept DNA; at least 10 micrograms is required.
iii) saliva in Oragene collection kit is accepted if unable to obtain blood (kits available upon request)

Test Request Form (TRF)

a) Completed CMDL TRF, with complete billing information is required for each specimen.
b) Clinical note/pedigree is recommended.

Order Codes (BRCA1/2)	***CPT Codes***	***TAT***
BRCA1/2-COMP (BRCA1 and BRCA2, next generation sequence analysis and deletion/duplication analysis)	81162, G0452	2 wks
BRCA1/2-AJ [BRCA1 and BRCA2 genes, targeted analysis for Ashkenazi Jewish common mutations: c.68_69delAG (BRCA1), c.5266dupC (BRCA1), and c.5946delT (BRCA2)]	81212, G0452	2 wks
BRCA1/2-DEL (BRCA1 and BRCA2 genes, deletion/duplication analysis)	81213, G0452	2 wks
BRCA1-CAS (BRCA1 gene, known familial sequence variant)	81215, G0452	2 wks
BRCA2-CAS (BRCA2 gene, known familial sequence variant)	81217, G0452	2 wks
BRCA1-DEL-CAS (BRCA1 known or targeted deletion/duplication analysis)	81215, G0452	2 wks
BRCA2-DEL-CAS (BRCA2 known or targeted deletion/duplication analysis)	81217, G0452	2 wks

References

1. Claus EB, et al. *Cancer.* 1996;77(11):2318-24.
2. Peto J, et al. *J Natl Cancer Inst.* 1999;91(11):943-9.
3. Ford D, et al. *Am J Hum Genet.* 1998;62(3):676-89.
4. Petrucelli N, et al. BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer. 1998 Sep 4 [Updated 2013 Sep 26]. GeneReviews® [Internet]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1247/
5. Frank TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, Gumpper KL, Scholl T, Tavtigian SV, Pruss DR, Critchfield GC. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. J Clin Oncol. 2002;20:1480–90.