

Hereditary Breast Cancer via *CHEK2* Gene Sequencing – Test #714

Brief Description of Clinical Features: More than 1 million new cases of breast cancer occur each year worldwide, making it the most common malignancy among women. It is estimated that ~10% of these cases have a strong hereditary component. Hereditary Breast Cancer (HBC; OMIM 114480) refers to the familial occurrence of early-onset (prior to the age of 40), bilateral mammary carcinomas. Importantly, tumors from individuals with HBC tend to be of a much higher histological grade, when first detected, than tumors from sporadic age-matched breast cancer controls (Honrado et al. *Modern Pathology* 18:1305-1320, 2005). As a result, survival rate after treatment is two-fold lower for patients with HBC, compared to those with sporadic breast cancer (Lonning et al. *Ann Oncol* 18:1293-1306, 2007). Thus, identifying individuals with a high-risk for developing HBC allows for early detection of tumor formation in these individuals, and is predicted to increase the rate of patient survival.

Genetics: Mutations in a number of genes have been reported to significantly increase an individual’s likelihood for developing breast cancer (reviewed by Tan et al. *J Clin Pathol* 61:1073-1082, 2008). Among those, germline mutations in the Breast Cancer genes, *BRCA1* and *BRCA2*, appear to provide the highest relative risk, ~10- to 20-fold. Early-onset breast cancer is also a major component of the Li-Fraumeni Syndrome (LFS; OMIM 151623), and mutations in the LFS-associated gene *TP53* also provide a 10- to 20-fold increased risk for developing bilateral mammary carcinomas, in addition to other cancers. Mutations in the *CHEK2* gene (OMIM 609265) were also reported to cause a Li-Fraumeni-like syndrome (Bell et al. *Science* 286:2528-2531, 1999), although subsequent studies have indicated that *CHEK2* mutations are only very rarely found in patients with classic symptoms of LFS (Lee et al. *Cancer Res* 61:8062-8067, 2001). However, mutations in *CHEK2* have been frequently found in patients who have HBC but do not have detectable *BRCA1* or *BRCA2* mutations (Vahteristo et al. *Am J Hum Genet* 71:432-438, 2002; Meijers-Heijboer et al. *Am J Hum Genet* 72:1308-1314, 2003), indicating *CHEK2* mutations likely contribute to a significant fraction of non-*BRCA1/2* hereditary breast carcinomas. *CHEK2* encodes a protein kinase that protects the genome from ionizing radiation and genotoxic insults. To date, approximately 40 mutations have been reported throughout the *CHEK2* gene, and >95% are detectable by this DNA sequencing test (Human Gene Mutation Database, www.hgmd.cf.ac.uk).

Description of This Particular Test: This test involves bidirectional DNA sequencing of coding exons 2-16 of the *CHEK2* gene, plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence a single exon (Test #100; \$190) in family members of patients with a known mutation, or to confirm research results.

Reference Sequences: Genomic: NC_000022.10 mRNA: NM_001005735.1 Protein: NP_001005735.1 CCDS 33629.1

Indications for Test: This test is recommended for individuals diagnosed with early-onset bilateral mammary carcinomas and a family history of breast cancer and/or sarcomas, particularly those who do not have a detectable mutation in *BRCA1*, *BRCA2* or *TP53* genes. This test is specifically designed for heritable germline mutations and is not appropriate for the detection of somatic mutations in tumor tissue.

Sensitivity of Test: This test is predicted to detect pathogenic mutations in ~6% of women with non-*BRCA1/2* Hereditary Breast Cancer (Nevanlinna & Bartek *Oncogene* 25:5912-5919, 2006).

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2 - 3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price:	Sequencing of the <i>CHEK2</i> Gene:	\$ 890
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x16	83898 \$ 260	Sequencing x16 83904 \$ 400
Separation x1	83894 \$ 50	Interpretation/Report x1 83912 \$ 110

Accreditation: CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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